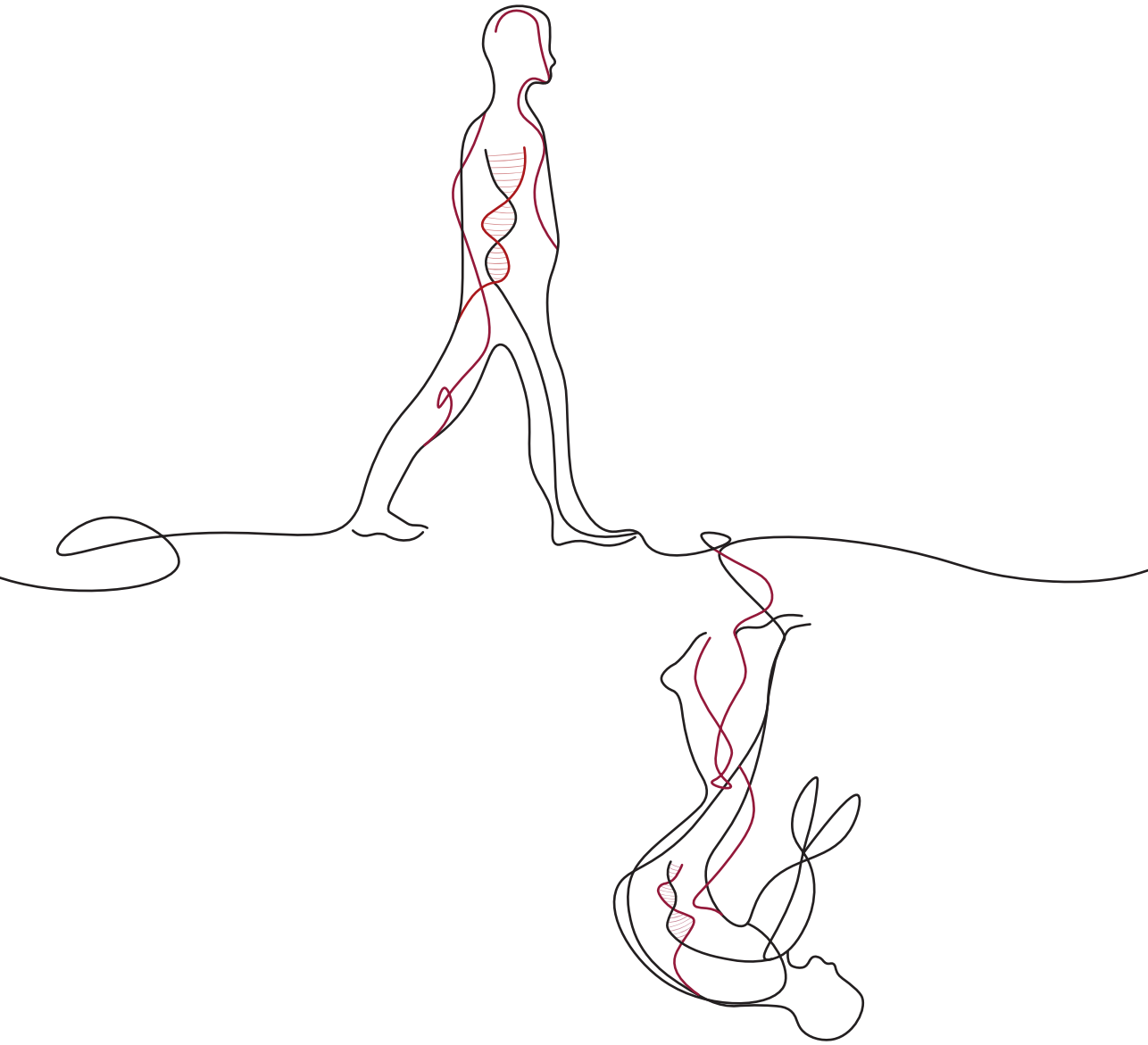
Invisible Scars

Unraveling the Epigenetic and Mental Health Consequences of Victimization



Bodine M.A. Gonggrijp

Invisible Scars:

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INVISIBLE SCARS

Unraveling the Epigenetic and Mental Health Consequences of Victimization

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Chapter 1.

General Introduction

Introduction

The impact of crime victimization has emerged as a critical issue in contemporary society, shaping not only public discourse but also the policies of criminal justice systems worldwide. Since the 1960s, many jurisdictions around the world have adapted their criminal justice systems to provide a stronger procedural position for victims of crime (Groenhuijsen & Letschert, 2006). One notable reform is the introduction of Victim Impact Statements (VIS), which began in 1976 in the United States and has since been implemented in several countries, including Canada Australia, New Zealand, the United Kingdom, and many European nations. VIS allows victims to submit written or oral statements to the judge during criminal cases, giving them a platform to share how the crime has affected them personally (Erez, 1991; Kragting et al., 2024). These reforms have provided victims with a voice in the legal process, empowering them to participate more actively in criminal proceedings. Another significant development in victim rights is the integration of compensation mechanisms within criminal procedure. In the Netherlands, victims are able to claim compensation for harm suffered, during the criminal proceedings, rather than having to file a separate civil suit. This shift simplifies the legal process for victims and provides quicker relief (Augusteijn et al., 2024). Such reforms reflect the growing recognition of the burden of crime victimization.

The increasing focus on victim rights has also led to the expansion of various support organizations that help victims cope with the aftermath of crime. In the Netherlands, for example, Slachtofferhulp Nederland (Victim Support Netherlands) and Fonds Slachtofferhulp (Fund Victim Support) offer practical, emotional, and legal support to victims, while the Schadefonds Geweldsmisdrijven (Violent Offences Compensation Fund) provides financial assistance to victims, particularly those who have suffered physical injury or trauma. These developments demonstrate a broader societal shift towards recognizing the potential lasting impacts of victimization and ensuring comprehensive support for victims.

Despite this heightened attention there still remain gaps in our understanding of the extent to which and mechanisms through which victimization affects individuals' long-

term physical and mental health outcomes. Crime victimization is often associated with long-term consequences that extend well beyond the immediate aftermath of the event. For example, victims more often than non-victims suffer from chronic pain, sleep disturbances, and an increased susceptibility to chronic diseases, which can severely impact their overall well-being (Basile et al., 2024; Basile et al., 2021; Britt, 2001; Chrisler & Ferguson, 2006; Turanovic, 2023). Crime victimization is also associated with enduring mental health challenges, such as depression, anxiety, and post-traumatic stress disorder (PTSD) (Bhavsar & Ventriglio, 2017; Bouffard & Koeppel, 2014; Burghart & Backhaus, 2024; Dworkin et al., 2017). Additionally, victimization has been linked to an increased risk of premature mortality, which may result from a range of factors, including homicide, suicide, victimization-related injuries, and the development of chronic diseases such as cardiovascular conditions (Adedokun & Burgess, 2012; Brown et al., 2009; Guha et al., 2020; Pridemore & Berg, 2017).

It is tempting to interpret the association of victimization and later outcomes as a causal one. But association does not equal causation and assuming causality overlooks significant complexities, such as perpetrator selection bias and confounding by third variables**.** Perpetrator selection bias occurs when offenders specifically target individuals who are perceived as more vulnerable—whether due to mental health challenges, social isolation, or reduced physical capacity. This selection process is likely driven by the perpetrator's attempt to minimize risk to themselves and maximize the likelihood of a successful crime. Rational choice theory supports this notion, suggesting that perpetrators make calculated decisions, weighing the costs and benefits of selecting a particular victim (Cornish & Clarke, 1989). Perpetrators are likely to choose targets who are less likely to resist or report the crime, thereby increasing their chances of success and minimizing the risks involved. This perpetrator selection bias may lead to an overestimation of the direct effects of victimization on negative health outcomes, as the individuals targeted may already be at greater risk for poor health, independent of the victimization itself.

Confounding by third variables further complicates the relationship between victimization and health outcomes. External factors such as socioeconomic status, family background, and pre-existing health conditions may independently influence both the likelihood of victimization and the development of negative outcomes. For example, individuals from lower socioeconomic backgrounds may have fewer resources to prevent victimization and to recover from its effects, potentially explaining the relationship between victimization and negative outcomes. Similarly, people with pre-existing mental health problems may be at increased risk of both being victimization and experiencing poor post-victimization outcomes, making it challenging to determine the true cause of harm.

In this dissertation I aim to distinguish between the effects caused by the victimization experience and the effects of other so called third, or confounding, factors. A design which enables such an investigation is a within family design, in particular if data from twins can be analyzed. I apply a discordant twin design that makes it possible to investigate latent confounding factors, namely genetic predispositions or shared environmental factors. The discordant twin design offers a unique methodological approach to untangle the causal influences from confounding by genetics or shared environment to provide deeper insights into the association between victimization and negative outcomes.

Unravelling Causal Relationships: The Role of Twin Studies in Victimization Research

In many areas of research, causality is determined through experimental designs where participants are randomly assigned to different conditions. The so-called randomized control trial (RCT) is one example of a strong experimental design. However, in victimization research, it is neither ethical nor feasible to control or manipulate who becomes a victim. As such, it is hard to assess the direct impact of crime victimization, independent of confounding. To address this problem, researchers turn to twin studies, which provide valuable insight by leveraging the natural genetic and environmental similarities between twins.

The classical twin study, is best known in behavioral genetics to disentangle the relative contributions of genetic and environmental factors to outcome traits and behaviors. By comparing the similarities and differences between monozygotic (i.e., MZ, identical) twins, who share 100% of their genes, and dizygotic (i.e., DZ, fraternal) twins, who share approximately 50% of their genes, researchers can estimate the relative influence of genetic factors (heritability) and shared or non-shared environmental factors in explaining population variation (Sahu & Prasuna, 2016).

Table 1.1 offers a summary of terminology and their explanations for the classical twin study. These provide insights into the heritability of traits and the influence of shared environments. A special application of the classical twin study is one that aims to establish causal relationships between specific exposures and outcomes. In observational research it is difficult to determine whether outcomes, e.g. mental health problems, are caused by exposures like victimization or by underlying predispositions (either genetic or environmental) that also increase the likelihood of encountering certain risks and becoming a victim. One type of twin study design provides a natural experiment where genetic and shared environmental factors are controlled when addressing the causes of an association, allowing us to better isolate the direct effects of victimization (Gesell, 1942; Goldberg & Fischer, 2014). This design is referred to as the **co-twin control design (CTCD).**

Application in Victimization Research

The CTCD is also known as the discordant twin design. This design involves identifying pairs of twins where one twin has experienced victimization, while the cotwin has not. Since the twins share either all genes (in the case of MZ twin pairs) or half of their genes (in the case of DZ twin pairs) and much of their prenatal and early environments, differences in outcomes between the victimized and non-victimized twins can be more confidently attributed to the experience of victimization rather than to underlying genetic or shared environmental factors, which are often confounding variables in traditional observational studies (van Dijk, Norris, & Hart, 2022; Vitaro, Brendgen, & Arseneault, 2009). This approach thus approximates the conditions of a randomized

Table 1.1. Behavioral-Genetic Terms and Notations Commonly Used in Twin Studies.

Term	Explanation
Monozygotic (MZ)	MZ twins arise from the same fertilized egg that splits and are genetically identical (i.e., they share 100% of their genetic material). They serve as a key comparison group in twin studies.
Dizygotic (DZ)	DZ twins develop from two separate eggs fertilized by two different sperm. They are no more genetically similar than typical siblings, and on average share 50% of their genetic material.
Heritability (h^2)	Heritability quantifies how much of the individual differences (variance) in a trait within a population are due to genetic factors, ranging from 0% (no genetic influence) to 100% (entirely genetic).
Shared Environment (c^2)	Proportion of variance within a population that is due to shared environmental factors. Shared environmental factors are those that make twins more similar to each other, such as parental socioeconomic status or household environment.
Non-Shared Environment (e^2)	Proportion of variance within a population that is due to unique environmental factors. Non-shared environmental factors refer to influences that differ between twins, such as different social groups, hobbies, or life events, and contribute to making them less similar.
Classical Twin Design (CTD)	By comparing MZ and DZ twins, researchers can estimate how much variation in a trait is due to genetic and how much to environmental factors. The CTD provides estimates of heritability, shared environment, and non-shared environment.
Co-Twin Control Design (CTCD)	The CTCD is used to distinguish between the confounding effects of shared genetic/environmental factors and the effects directly attributable to an external exposure, such as victimization.

experiment by inherently controlling for genetic and shared environmental variables, thereby strengthening causal inferences in situations where experiments are not feasible.

The CTCD in victimization research is relatively rare and has mainly focused on child or adolescent victimization and various outcomes (Dinwiddie et al., 2000; Matthews et al., 2022; Sartor et al., 2008; Schaefer et al., 2018). To the best of my knowledge, only two studies have explored the impact of adult crime victimization using the CTCD (Connolly et al., 2022; Piirtola et al., 2024). Both studies found evidence for a causal association between victimization and depression. However, these studies only focused on depression as an outcome, without examining other potential consequences of

victimization. More research is needed to understand how this methodology can help clarify the causal effects of crime victimization on mental and other health outcomes. In this dissertation, I will apply the CTCD to examine mental health outcomes, including depression, anxiety, and loneliness, as well as general self-reported health, to provide a more comprehensive understanding of the impact of victimization.

Exploring Protective Factors

While the CTCD can help establish the causal impact of victimization on later outcomes, it is equally important to explore factors that may buffer individuals from adverse outcomes, whether the relationship is causal or associative. Understanding such protective factors can inform prevention and intervention strategies aimed at minimizing the negative consequences of victimization. One such factor is social support, which has consistently been shown to play a key role in mitigating mental health problems.

Social support is broadly defined as '*the provision of assistance or comfort to others, typically to help them cope with biological, psychological, and social stressors*' (American Psychological Association, n.d.). It can encompass emotional support (empathy, care), instrumental support (tangible assistance), and informational support (guidance or advice), all of which may contribute to resilience and healing following traumatic experiences (Dutton & Greene, 2010; Hirai et al., 2020).

The buffering hypothesis suggests that social support can mitigate or "buffer" the negative effects of stressful events on an individual's mental health (Cohen & McKay, 2020). According to this hypothesis, social support reduces the impact of stressors by providing resources that help individuals cope more effectively, thereby lessening the likelihood of adverse outcomes such as depression or anxiety. Social support may thus act as a protective buffer, helping victims of crime cope better with the aftermath by fostering a sense of belonging and reducing feelings of isolation. It also facilitates recovery by encouraging adaptive coping strategies, providing emotional validation, and reducing physiological stress responses. Social support can also be a protective factor in and of itself, safeguarding against negative mental health outcomes regardless of victimization, as research has consistently demonstrated that individuals with strong

social support networks tend to experience fewer mental health issues, such as depression, anxiety, and PTSD (Harandi, Taghinasab, & Nayeri, 2017; Kaniasty & Norris, 2008).

In this dissertation, I will examine social support as a mitigating factor when investigating the impact of victimization, assessing its potential to reduce the severity of negative mental health outcomes and promote resilience in affected individuals. This is important because identifying factors that can promote resilience is necessary for improving post-trauma outcomes and for developing evidence-based interventions that enhance recovery.

Epigenetics

While victimization has been consistently associated with mental and physical health problems, the question arises about the biological pathways that may explain these long-term health issues. While multiple factors may contribute to the complex interplay between exposure to victimization and long-term health outcomes, one important area of focus is **epigenetics**. See Table 1.2 for commonly used terms in epigenetics research and their explanations.

The field of epigenetics studies how gene activity is regulated. DNA, or deoxyribonucleic acid, is composed of a sequence of nucleotide bases (A, C, G, T) that serve as the fundamental code for building and maintaining the human body. This sequence provides the instructions for synthesizing proteins or for regulation of gene activity. These genetic instructions, inherited from our parents, remain largely unchanged throughout life. However, gene expression — the activation of information encoded in DNA at a particular time — can change over the lifetime and is influenced by factors such as environmental exposures and life experiences (Boyce et al., 2021; Dolinoy, Weidman, & Jirtle, 2007; McCaw, Stevenson, & Lancaster, 2020; Vaiserman, 2015). These factors can influence gene expression through the epigenome. Whereas the DNA sequence is the same in each cell in our body, they all have their own unique epigenome, which is a collection of chemical modifications that dictate which genes are active or silent in that particular cell. In other words, the epigenome acts as a set of instructions that tells each cell how and

Table 1.2. Key Terms in Epigenetics

Term	Explanation
Epigenetics	The study of how gene activity is regulated by chemical modifications that do not alter the DNA sequence itself.
DNA	Deoxyribonucleic Acid. The molecule that carries the genetic instructions used for the growth, development, and functioning of all living organisms. DNA is composed of a sequence of nucleotide bases.
DNA Sequence	The genetic code of an individual, consisting of nucleotide bases (adenine, thymine, cytosine, and guanine) in a molecule of DNA. This sequence encodes genetic information.
RNA	Ribonucleic Acid. A molecule that plays a role in translating the genetic information stored in DNA into proteins.
Epigenome	A collection of chemical modifications, such as DNA methylation, that regulate gene expression without changing the underlying DNA sequence.
DNA Methylation	An epigenetic mechanism that involves adding a methyl group (CH_3) to the DNA, usually at CpG sites, which can suppress gene expression.
CpG Sites	Regions in DNA where a cytosine (C) is followed by a guanine (G). These sites are often targeted for DNA methylation, which can affect gene activity.
Epigenetic Clocks	Biomarkers that estimate age based on DNA methylation levels at specific CpG sites.
Epigenetic Age Acceleration	A situation where an individual's biological age (as measured by epigenetic clocks) is higher than their chronological age, indicating faster biological aging.
Epigenetic Age Deceleration	A situation where an individual's biological age (as measured by epigenetic clocks) is lower than their chronological age, indicating slower biological aging
Hannum	A first generation epigenetic biomarker primarily focused on blood tissue samples, which estimates biological age based on methylation patterns at specific CpG sites.
Horvath	A first generation epigenetic biomarker which is more versatile than the Hannum biomarker because it can predict biological age across multiple tissues and cell types, not just blood.
DNAmPhenoAge	A second generation epigenetic biomarker developed by incorporating physiological markers and DNA methylation data, used to predict lifespan and aging-related diseases.
GrimAge	A second generation, more comprehensive epigenetic biomarker that incorporates factors like smoking history and sex, providing a more accurate prediction of morbidity and mortality.
DunedinPACE	A third generation biomarker that measures the pace of aging by analyzing changes across multiple physiological systems, providing an estimate of aging rate.

when to use its genetic information, enabling the vast variety of cell functions in the body and allowing cells to respond to changing environmental conditions.

There are multiple epigenetic mechanisms. In human epidemiological studies, DNA methylation is the most commonly studied mechanism, because it is considered one of the most stable and because it can be measured in large samples. DNA methylation involves the addition of a methyl group — a small molecule composed of one carbon atom and three hydrogen atoms (CH_3) — to the DNA molecule. Methylation typically occurs at specific regions in the DNA called CpG sites, where a cytosine (C) is followed by a guanine (G). These sites are common targets for methylation and play an important role in regulating gene expression. DNA methylation can suppress gene expression by blocking access to the DNA, preventing the gene from being transcribed into RNA (ribonucleic acid). There are several roles for RNA, including translating the genetic sequence information into proteins or regulating gene expression. Because the epigenome can respond to environmental exposures (Grant, 2023), it is one path along which external experiences like stressful life experiences such as victimization can lead to long-lasting biological effects. Recent studies on the impact of stress on epigenetic profiles have focused on epigenetic biomarkers of ageing, and reported that stress is associated with accelerated biological ageing (Harvanek et al., 2021; Wu et al., 2024).

Biological Aging and Epigenetic Biomarkers

Based on DNA methylation data, multiple indices of biological aging have been developed. These biological markers, often referred to as “epigenetic clocks”, are calculated based on algorithms that estimate an individual's DNA methylation age, a measure of biological age, based on the methylation levels at specific CpG sites in the DNA (Raffington & Belsky, 2022). When an individual's DNA methylation age deviates from their chronological age, this deviation is referred to as *epigenetic age acceleration* or *deceleration*, indicating increased or decreased biological aging, respectively. Epigenetic age acceleration has been linked to increased mortality risk (Marioni, Shah, McRae, Chen, et al., 2015) and a range of adverse health outcomes, such as cognitive impairment and poor physical and cognitive fitness.

The first-generation biomarkers, such as those developed by Hannum and Horvath, were effective in predicting chronological age but had limited accuracy in predicting age-related conditions like disease and functional decline (Bell et al., 2019; Hannum et al., 2013; Horvath, 2013). To improve predictive power, next-generation epigenetic biomarkers like PhenoAge and GrimAge were developed. PhenoAge was initially developed as an overall score that predicts lifespan, based on multiple clinical physiological markers of aging. Later, a DNA methylation based surrogate for PhenoAge was developed (DNAmPhenoAge). GrimAge builds on this approach by also including factors such as age, sex, and smoking history, providing a more comprehensive measure of biological aging. These newer biomarkers have shown greater accuracy in predicting morbidity and mortality (Levine et al., 2015). Additionally, a pace of aging biomarker has been developed; the DunedinPACE biomarker. The DunedinPACE biomarker, focuses on the rate of aging and was trained on longitudinal changes across multiple physiological systems, providing an estimate of the rate at which these systems are aging in an individual (Belsky et al., 2022; Raffington & Belsky, 2022). The scale of the Hannum, Horvath, PhenoAge, and GrimAge biomarkers is interpreted as biological age in years, whereas the DunedinPACE biomarker represent the pace of aging within one chronological year. These, at present most frequently examined, epigenetic biomarkers in epidemiological research thus all address slightly different aspects of biological aging and the aging process, with some focusing on chronological age and others on the rate of physiological decline. I therefore included them all when assessing the potential impacts of stressful life events, including victimization, on biological aging in this dissertation.

My research required twin data on victimization, life events, social support, mental health, and epigenetics. The number of participants should be large to ensure statistical power and the ability to generalize findings. To explore -as a first step- associations in the general population, the study design would be strengthened if data on non-twins were collected in a similar manner. I therefore turned to the Netherlands Twin Register (NTR), a rich and comprehensive national resource for studying genetic and environmental factors.

Netherlands Twin Register

The NTR is a comprehensive national resource that has been collecting longitudinal data on twins and their family members since it was established in the late 1980s by Orlebeke and Boomsma, with the goal of studying the influence of genetic and environmental factors on human development, behavior, and health (Boomsma, Orlebeke, & Van Baal, 1992). Since its inception, the NTR has enrolled over 120,000 twins and their family members, including siblings, parents, and spouses. The register collects extensive longitudinal data across a wide range of phenotypes through surveys and biological samples (Boomsma et al., 2006; Ligthart et al., 2019; Willemsen et al., 2010; Willemsen et al., 2013). Participants have contributed data on lifestyle, demographics, health and behavioral traits through surveys conducted every two to three years. In 2000, 2002, 2004 and 2009 the surveys assessed the occurrence of life events, including victimization (Geels et al., 2013; Middeldorp et al., 2005). In several projects, the NTR has gathered biological samples, including DNA from buccal cells and blood, creating an invaluable biobank for genetic and epigenetic research (Sirota et al., 2015; Van Asselt et al., 2023; Van Dongen et al., 2016). Research enabled by the NTR has contributed to a wide range of fields, including behavioral and psychiatric genetics, epidemiology, and health psychology, helping to clarify the genetic and environmental bases of traits such as mental health disorders, physical health outcomes, and cognitive development (Boomsma, Busjahn, & Peltonen, 2002). For my work, the NTR provided the ideal dataset, offering a large number of participants with detailed data on the variables crucial to my analyses. The availability of biological samples, combined with the extensive survey data on life events, mental health, and social support, made it an invaluable resource for investigating the complex relationships between victimization, life events, and health outcomes. The variables examined in this dissertation, along with the instruments and sample sizes, are detailed in Table 1.3.

Table 1.3. Overview of the Exposure and Outcome Measures and Total Sample Sizes Examined in this Dissertation.

Variable	Instrument	Assessed in year
Victimization	Self-reported survey data: '*What events have happened to you in your life?*' Participants selected from victimization three categories: property offences (theft, burglary, and vandalism); violent crime (robbery, physical violence); sexual crime (rape, sexual assault).	2000, 2002, 2004, 2009
Negative Life Events	Self-reported survey data: Self-reported survey data: '*What events have happened to you in your life?*' Participants selected from a range of life events, including victimization.	2009
Depression	Adults Self Report (ASEBA, 2023)	2002, 2004, 2009
Anxiety	Spielberger Trait-Anxiety Inventory (Boomsma et al., 2000).	2000, 2002, 2009
Loneliness	Three-Item Loneliness Scale (Hughes et al., 2004).	2000, 2004, 2009
Self-Reported Health	Single item: '*In general, how would you rate your health?*'.	2009
Social Support	Duke–UNC Functional Social Support Questionnaire (Broadhead et al., 1988).	2009
Epigenetic Biomarkers	DNA methylation in blood (Illumina 450K / Epic arrays).	2004–2008, 2010–2011

Outline of Dissertation

In this dissertation I investigate the psychological and biological consequences of crime victimization, focusing on how genetic and environmental factors influence these outcomes. I apply the CTCD to assess mental health, the role of social support, and epigenetic aging as a consequence of crime victimization.

In **Chapter 2** the CTCD is presented and scripts for data simulation are provided, along with practical guidance and accompanying scripts for implementing the CTCD in R, SPSS, and Stata. This chapter provides an overview of the strengths and limitations of the CTCD and discusses the analysis methods for binary and continuous outcome and exposure variables.

Chapter 3 applies the CTCD to investigate the relationship between crime victimization and mental health outcomes, namely depression, anxiety, and loneliness. This chapter tests whether these associations are confounded by genetic and/or environmental factors.

Chapter 4 shifts the focus to social support by examining its genetic influence, challenging the traditional view of social support as purely environmental. This chapter offers an estimate of the heritability of social support, and also tests for the contribution of shared environment and potential sex differences.

Chapter 5 examines whether social support buffers or protects against the negative impact of crime victimization on mental and self-reported health outcomes. This is examined by testing both the main effect and the moderating effect of social support, while controlling for genetic and shared environmental confounders.

The last part of this dissertation explores biological consequences of stressful experiences. **Chapter 6** tests the impact of negative life events on epigenetic aging. This chapter looks at the effects of ever experienced specific negative life events, such as the loss of a loved one, crime victimization and financial problems, as well as the cumulative number of negative life events experienced, on epigenetic aging.

In **Chapter 7** the focus is on the relationship between victimization of violent, sexual, and property crimes, and biological aging. This chapter extends the findings from Chapter 6 by investigating polyvictimization and both lifetime and recent crime victimization experiences.

Together, these chapters aim to provide an understanding of how victimization impacts mental health, physical health, and biological aging, while controlling for genetic and shared environmental factors.

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Chapter 2.

Co-Twin Control Design: Implementation and Methodological Considerations

Abstract

Establishing causal relationships in observational studies is an important step in research and policy decision making. The association between an exposure and an outcome can be confounded by multiple factors, often making it hard to draw causal conclusions. The Co-Twin Control Design (CTCD) is a powerful approach that allows for the investigation of causal effects while controlling for genetic and shared environmental confounding factors. This paper introduces the CTCD and offers an overview of analysis methods for binary and continuous outcome and exposure variables. Tools for data simulation are provided, along with practical guidance and accompanying scripts for implementing the CTCD in R, SPSS, and Stata. While the CTCD offers valuable insights into causal inference, it depends on several assumptions that are important when interpreting CTCD results. By presenting a broad overview of the CTCD, this paper aims to equip researchers with actionable recommendations and a comprehensive understanding of the design's strengths and limitations.

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The Co-twin Control Design: Implementation and Methodological Considerations

Establishing and quantifying the causal effect of an exposure on an outcome trait is a major goal in many fields of research. Causal inference plays a pivotal role in- and outside science. It advances our understanding of the complex relationships between exposures and outcomes, informs public health interventions, and shapes policy decisions. Exposures and outcomes can both refer to a wide array of variables, including external environmental impact, comprehensive lifetime exposure records, individual traits, disorders, or diseases. In observational studies, unraveling causal relationships is challenging. The association between an exposure and an outcome can be confounded by multiple factors, leading to spurious associations, and potentially incorrect causal inference. Confounders, if identified a priori and observable (measurable), can be included in the analysis of causal relations. However, it is hard to rule out unobserved, possibly latent, confounders. Genetic confounding, for instance, arises when genes influence the exposure and the outcome, independent of a causal relationship (horizontal pleiotropy; Solovieff et al. (2013). If the genes involved in the confounding are unknown, which is often the case in studies of genetically complex traits, the confounding is latent. Failing to account for confounding variables can result in erroneous causal inference ((Sjölander et al., 2012). This highlights the need for robust methods that can help account for confounding factors in observational studies.

Family-based designs, including co-twin control design (CTCD) or discordant twin-pair design, were developed to investigate causal relations in the presence of latent confounding. The CTCD utilizes data of discordant monozygotic (MZ) twin pairs to examine the association between an exposure and an outcome variable (Gesell, 1942). One of the earliest experiments to implement a CTCD was conducted in 1927 when a pair of identical twins were taught to climb stairs at different time intervals. Twin A underwent a 6-week training period at 46 weeks old and managed to climb the stairs in 26 seconds. Twin B, on the other hand, climbed the stairs in 45 seconds without any training. Subsequently, Twin B received training for 2 weeks and improved her time to 10

seconds, despite having a much shorter training duration compared to her co-twin. By the time they reached 56 weeks and 3 years, their performance on the staircase was similar. This study's findings established an association between learning and maturity (Gesell & Thompson, 1943).

In observational data, the CTCD is applied to discordant MZ twin data when one twin has been exposed to a condition or variable of interest and the other has not. For example, one twin is a smoker and the other is not, or one twin was the victim of a crime and the other was not. Discordance can also be for disorders and diseases such as MS (multiple sclerosis), cancer or psychiatric conditions. Discordancy is not limited to binary exposures. MZ twins may differ with respect to continuous exposures such as birth weight (Groen-Blokhuis et al., 2011) or body mass index (van Dongen et al., 2015). The major advantage of the CTCD is the inherent matching on genetic and shared environmental confounders. Specifically, MZ twins are genetically identical, or nearly identical, and have shared many environmental influences including intrauterine exposures. In addition, MZ twins are perfectly matched for age and sex. The inclusion of discordant dizygotic twins (DZ) who are likewise matched for age and sex (in the case of same-sex DZ twins), and shared environment also is informative, as are designs with full siblings. However, DZ twins and siblings are not perfectly matched for genetic factors, as they shared on average 50% of their alleles, and so are not genetically identical. Thus, the CTCD, applied to MZ twins corrects for genetic and shared environmental confounding, and confounders directly associated with age and sex. There are other family-based designs that can be applied, including a sibling design, but only the analysis of data from MZ twins, who are nearly genetically identical, controls for genetic confounding (D'Onofrio et al., 2013). It is worth noting that in rare cases MZ twins inherit very similar, but not entirely identical, genotypes. In such cases, discordant MZ twins can be valuable in identifying specific genetic mutations (post zygotic) that may be causing the differences. For instance, a study conducted by Kondo et al. (2002) successfully identified the interferon regulatory factor 6 gene (IRF6) as the locus responsible for the development of Van der Woude syndrome (VWS) in a pair of MZ twins discordant for VWS.

Table 2.1. Overview of papers focusing on the CTCD and their additional value.

Author	Year	Title	Focus
Christian & Kang	1972	Efficiency of Human Monozygotic Twins in Studies of Blood Lipids	Extensive comparison of the paired and unpaired design, including the efficiency of both the designs, and estimation of the experimental error for studies involving twins versus unrelated subjects.
Martin et al.	1982	Co-Twin Control Studies: Vitamin C and the Common Cold	Provides an introduction of the CTCD and discussion of the advantages as well as an application of the CTCD to study the effect of vitamin C on cold symptoms.
Hu et al.	1998	Modelling ordinal responses from co-twin control studies	Ordinal data in a CTCD by investigating the applicability of the random-effects and GEE approaches.
Lichtenstein et al.	2002	The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies	Step-by-step description of the discordant twin design.
Goldberg & Fisher	2005	Co-twin Control Methods	The basic analytic methods that can be applied to CTCD with a (dichotomous) discordant environmental risk factor and a continuous or dichotomous outcome variable are given.
Madsen & Osler	2009	Commentary: Strengths and limitations of the discordant twin-pair design in social epidemiology. Where do we go from here?	Discussion of the strengths and limitations of the CTCD.
Vitaro et al.	2009	The discordant MZ-twin method: One step closer to the holy grail of causality	Presents two analytical strategies based on the discordant MZ twin method; the difference score strategy and mixed strategy.
Mcgue, Osler & Christensen	2010	Causal Inference and Observational Research: The Utility of Twins	Methods of causal inference are discussed, with a focus on the discordant twin design.

Table 2.1. Continued.

Author	Year	Title	Focus
Van Dongen et al.	2012	The continuing value of twin studies in the omics era	Review that considers the continuing value of twin studies in the current era of molecular genetic studies.
Sjölander et al.	2012	Analysis of 1:1 Matched Cohort Studies and Twin Studies, with Binary Exposures and Binary Outcomes	An overview of methods for matched cohort and twin studies with binary exposures and outcomes.
D'Onofrio	2013	Critical Need for Family-Based, Quasi-Experimental Designs in Integrating Genetic and Social Science Research	Discusses major advantages, limitations, and assumptions of family-based quasi-experimental designs for examining environmental risks.
Røysamb & Tambs	2014	The beauty, logic and limitations of twin studies	Central theoretical foundations of the classic and extended twin designs are discussed, including the CTCD.
Sahu & Prasuna	2016	Twin Studies: A Unique Epidemiological Tool	A general overview of twin studies is given and the steps of the co-twin control analyses with recommended software packages.
Segal	2019	Co-Twin Control Studies: Natural Events, Experimental Interventions and Rare Happenings/Twin Research	Issues of the CTCD are discussed with reference to earlier studies.
McAdams et al.	2021	Twins and Causal Inference: Leveraging Nature's Experiment	Review discussing how monozygotic and dizygotic twin pairs can be used to strengthen causal inference.
van Dijk et al.	2022	Using Twins to Assess What Might Have Been: The Co-twin Control Design	Description of the CTCD, including statistical framework, value and limitation, and example code for SAS and R.

The Current Study

The CTCD has generated substantial interest and has led to multiple methodological and review papers. Table 2.1. contains a brief description of these papers and their scope. The aim of the current paper is to provide an overview of the CTCD with a focus on its application to data from large twin registries and summarize the methodological considerations. We discuss the analysis of binary and continuous exposures and

outcome variables. We add to the existing literature summarized in Table 6.1 by presenting simulation analyses that illustrate various scenarios encountered in the CTCD, such as different sources of confounding factors (e.g., no confounding, genetic confounding, shared environmental confounding). Additionally, we offer a collection of scripts that can be readily utilized with popular statistical software packages such as SPSS, R, and Stata.

Co-Twin Control Analyses Design

The CTCD, as applied to MZ and DZ twin pairs typically involves three steps, as outlined by Lichtenstein et al. (2002). The first step focuses on a total sample. We assume that the sample is representative of the general population, which is likely to be the case in population-based twin registries. The second step focuses on DZ twins, while the third step concentrates on MZ twins. We outline these steps in more detail below.

Step 1: Test for the association at the population level between exposure and outcome

In this first step, the exposed individuals are compared to all non-exposed individuals (i.e., controls) to examine the association between the exposure and the outcome. Thus, the relationship between exposure and outcome is assessed in all participants in the sample, without considering twin status. Cases can come from non-twins (if included in the sample), discordant twin pairs, or pairs that are concordant for exposure. When analyzing data from twin registries the total sample includes data from related individuals, thus it is necessary to correct for familial clustering since the assumption of independent observations is otherwise violated.

Subsequent steps focus exclusively on DZ and MZ twin pairs. These steps aim to investigate the presence of familial and genetic confounding in the association between the exposure and outcome variables.

Step 2: Matched analysis in same-sex dizygotic (DZ) twin pairs.

In the second step, a within-pair analysis is conducted in DZ exposure–discordant twin pairs. Often, only same-sex DZ twins are considered. However, opposite-sex twins can be

included, and in cases where the research hypothesis specifically relates to sex as a potential cause of the association under investigation considering opposite-sex twins is an optimal design. For example, Cui et al. (2005) conducted a study on birth defects in a sample of 4,768 opposite-sex twins, aiming to examine potential sex differences. The findings revealed that among the opposite-sex twin pairs, males exhibited a 29% higher risk of birth defects compared to their twin sisters.

DZ twins and non-twin siblings share on average 50% of their segregating alleles, whereas MZ twins share 100% of their alleles. Both MZ and DZ twins share certain environmental factors, such as shared family experiences, and early intrauterine exposures, such as maternal smoking during pregnancy. A within-DZ twin pairs analysis controls for shared environmental factors that were not accounted for in the population-level analyses.

Step 3: Matched co-twin analysis in the monozygotic twin pairs

The analysis of step two is repeated for the exposure–discordant MZ twin pairs. Given the aim of controlling for confounders, the analyses of exposure–discordant MZ twins is the most powerful, given the matching for sex, age, genetic influences, and shared environmental influences. Note that in studies that target rare diseases or involve large-scale omics measurements in biological samples, such as epigenetic profiles in blood, often only this third step is conducted. In such cases, researchers actively seek pairs of MZ twins where one twin is affected by the disease, trait, or exposure of interest, while the other twin remains unaffected or only the most extreme discordant twin pairs are selected. For example, a study by Dempster et al. (2014) revealed distinct DNA methylation differences in 18 pairs of MZ twins discordant for adolescent depression. Another example is the study by van Dongen et al. (2015) where only twin pairs BMI were selected (N=120 pairs) who were extremely discordant for BMI. The result supported causal effects of obesity, as the heavier twin had a more unfavorable blood biomarker profile than their leaner co-twin.

Evaluating results across the three steps

As explained, the CTCD tests the relationship between exposure and outcome in individuals who differ in their exposures in the population sample (step 1), within DZ twin pairs who are discordant for the exposure (step 2), and within discordant MZ twin pairs (step 3). To support a causal hypothesis, we inspect the strength of these relationships. The associations within the population (step 1, see above) may be confounded by genetic or environmental factors. Associations within DZ twin pairs discordant for exposure (step 2) control for shared environmental effects, and associations within MZ twin pairs discordant for exposure (step 3) control for both shared environmental and genetic effects.

Figure 2.1 illustrates four scenarios resulting from these three steps. In scenario A, where exposure causally affects the outcome, we expect to observe associations at the population level and within discordant twin pairs. For example, if victimization of a crime causes depression, the victims and non-victims in the population will differ in depression status, and a similar difference will be observed within discordant twin pairs. However, this pattern is necessary, but not sufficient, evidence of causality since non-shared environmental factors are not accounted for by the CTCD design.

Scenario B represents the case where the association between exposure and outcome is entirely explained by genetic confounding. While an association is expected to be observed at the population sample level, it is expected to be zero within the MZ pairs, as the genetic factors that confound the association are identical between the twins. The association within discordant DZ twin pairs will be intermediate, with the exact effect size depending on the size of the genetic covariance between the exposure and outcome variable and the variance of the exposure variable.

Scenario C depicts shared environmental factors as the sole confounder. Associations between exposure and outcome are again expected to be observed at the population level, but absent within both DZ and MZ twin pairs, as the shared environment is equal in both types of pairs. Finally, scenario D suggests partial confounding by genetic and environmental factors. Associations would be reduced within DZ twin pairs and further

reduced within MZ pairs compared to the population-level effect. The presence of an exposure effect within discordant MZ pairs supports at least a partial causal effect.

Statistical Approaches

Multiple statistical approaches have been developed to estimate the association between exposure and outcome in the three steps outlined above. An overview of commonly applied analyses is presented in Table 2.2. We note that Table 2.2 does not provide an exhaustive overview of all possible analyses but aims to summarize some common approaches.

One point to emphasize is that in twin data analysis, the inclusion of twin pairs in the analysis relies on their discordance in both exposure level and outcome variables. If the outcome or exposure variable is the same within a twin pair, it indicates a lack of within-pair variation. Consequently, such twin pairs do not contribute information. Thus, only twin pairs discordant for the exposure and outcome variable contribute to the estimation of the association between the exposure and outcome (Frisell et al., 2012). While this phenomenon of exclusion is often discussed in relation to binary variables, where many twin pairs may share the same exposure or outcome values, it is not limited to binary

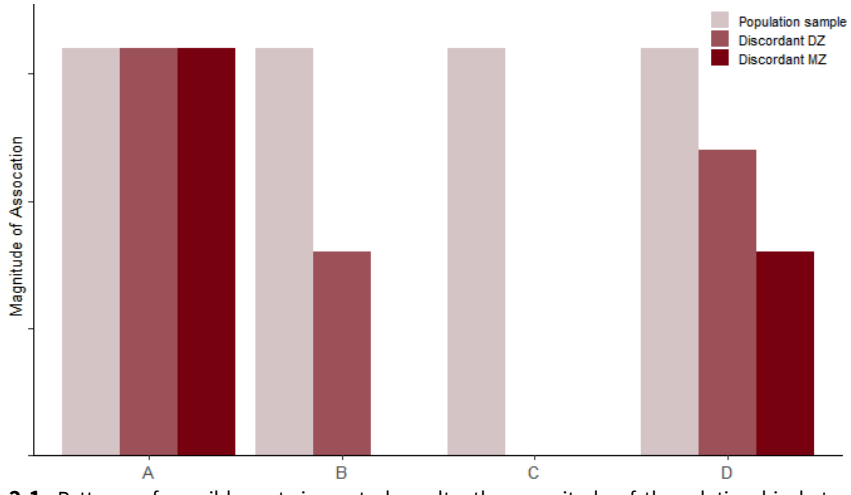

Fig 2.1. Patterns of possible co-twin control results: the magnitude of the relationship between exposure and outcome at the population level, and within discordant dizygotic (DZ) and monozygotic (MZ) twins under different scenarios. Scenario A = no confounding, B = solely genetic confounding, C = solely shared environmental confounding, and D = partial genetic and shared environmental confounding. The Y-axis depicts the magnitude of the association, e.g. a regression coefficient.

Table 2.2. Possible statistical models for the population and discordant twin analyses for both binary and continuous variables.

			Outcome	
			Binary	Continuous
Population analysis	Exposure	Binary	Logistic regression	Linear regression Two-sample t-test Anova
		Continuous	Logistic regression	Linear regression
Discordant twin analysis	Exposure	Binary	McNemar's test Conditional logistic regression	Fixed effects regression Paired t-test
		Continuous	Conditional logistic regression	Fixed effects regression

data. In the case of continuous variables, twins can be concordant, i.e., share the same values (e.g., have the same height). Thus, in both continuous and binary data, twin concordance on the exposure or outcome results in the exclusion of twin pairs, and the true sample size in these analyses is given by the number of discordant twin pairs for the exposure as well as the outcome.

Outcome Variable: Binary

Analyses of binary outcomes often focus on odds ratio estimates (OR). An OR of 1 indicates no association, while ORs below 1 or above 1 indicate decreased or increased odds of the outcome with increasing exposure, respectively (Moser & Coombs, 2004).

In population sample analyses, logistic regression models adjusted for covariates are often employed to analyze binary outcomes. If there is clustering in the data because of related participants a correction for clustering is necessary, for example by mixed models with random effects or a generalized estimating equation approach (GEE). In discordant twin analyses with continuous exposure and binary outcome variables, conditional logistic regression analyses (CLR) are common, accounting for stratification and matching (Graubard & Korn, 2011; Sjölander et al., 2012). For example, Kendler and Gardner (2010) analyzed data from 4910 female and male twins by CLR to investigate the association between dependent stressful life events and major depression (MD). They found a strong association between dependent stressful life events and MD in both female and male twins. The association was lower in dizygotic (DZ) twins and lower still in monozygotic (MZ) twins, suggesting confounding by genetic factors.

When the exposure and outcome variables are binary, an alternative approach for discordant twin analyses is provided by McNemar's test. This test is based on the 2x2 contingency table of matched responses to determine if there are statistically significant differences in a dichotomous dependent variable between two related groups (Adedokun & Burgess, 2012). For instance, Romanov et al. (2003) employed McNemar's test in a study of 9,947 Finnish adult twins and found that the effect of life events on depression was similar in both MZ and DZ twins discordant for depression, indicating that the relationship between experiencing multiple life events and depression is not due to genetic and shared environmental confounding.

Outcome Variable: Continuous

For continuous outcome variables, there are several modeling options for population analyses. One common approach is to use linear regression models, which may include measured covariates. Correction for clustering may be necessary using mixed models with random effects for clustering factors such as family and zygosity of twins, or a generalized estimating equation (GEE) approach.

In discordant twin analyses, a fixed effect regression analysis can be conducted. This involves regressing the within-pair difference on the continuous outcome variable on the within-pair difference on the exposure variable. An example of this approach is demonstrated in the study by Middeldorp et al. (2008), which examined the associations of life events with anxious depression and personality in data from 5,782 monozygotic (MZ) and dizygotic (DZ) twins participating in longitudinal survey studies in the Netherlands. The findings did not provide evidence to support a causal hypothesis, as there were no differences in anxious depression, neuroticism, and extraversion scores between exposed and non-exposed unrelated subjects and within discordant MZ and DZ twin pairs.

When both the exposure and outcome variables are continuous, often studies create two groups based on the continuous exposure variables to determine discordance between twins. For example, Groen-Blokhuis et al. (2011) investigated the association between low birth weight and attention problems. They classified twin pairs as discordant for

birth weight if the birth weight of the smaller twin was at least 15% lower than the birth weight of the larger twin or if there was a birth weight difference of at least 400 grams. Children with lower birth weights had higher scores on hyperactivity and attention problems compared to children with higher birth weights. Similar findings were observed for unrelated pairs, as well as MZ and DZ twin pairs, providing evidence for a causal relationship between birth weight and attention problems. However, we note that this method of classification results in a loss of information. An alternative approach is to use the original scores of the exposure variable in the analyses, without dichotomizing it.

Statistical Approaches Simulation

A data simulation was conducted using R to demonstrate the application of the CTCD for assessing causality and confounding. Three datasets were generated: one for a population sample, one for a dizygotic (DZ) twin sample, and one for a monozygotic (MZ) twin sample, where the desired samples can be specified by the user. Note that when either the exposure variable or the outcome variable is binary, only the discordant twin pairs with respect to both the exposure and outcome will be included in the analyses, resulting in a reduced sample size for MZ and DZ pairs. The script for the data simulation can be found in the Github repository (*https://github.com/bmagonggrijp/CTCD-Implementation-and-Methodological-Considerations).* The simulation implemented the scenarios depicted in Figure 2.1. for each group (population, DZ twins, and MZ twins). Normally distributed continuous variables were generated for both the exposure (x) and the outcome (y) variables by exact data simulation. Subsequently, binary variables (dx and dy) were derived from the continuous variables. All continuous values above zero were assigned a value of one, indicating a positive outcome ('case'), while the remaining values were assigned a value of zero ('control'). The simulation scenarios can be customized to incorporate different strengths of association and genetic and non-genetic variance components of x and y based on specific simulation requirements.

In the current simulation, the variance components for x and y were chosen based on an ACE model (i.e., in this model the variation in a phenotype is due to additive genetic

effects (A), the common environment (C), and the unique, random, environment (E)) with a relatively small contribution of C. The simulated exposure variable was based on traits such as victimization, with variance components of a2 = .45, c2 = 0.22, and e2 = 0.33 (Beaver et al., 2009), while the simulated outcome variable represented a trait such as depression, with variance components of a2 = 0.40, c2 = 0.10, and e2 = 0.50 (Huider et al., 2021; Sullivan, Neale, & Kendler, 2000).

Twin correlations and cross-twin cross-trait correlations, either Pearson or tetrachoric correlations, are summarized in Supplementary Table 2.1. Additionally, the correlation between the difference scores of MZ and DZ twins for 2 traits is presented in Supplementary Table 2.1.

Analyses of Simulated data in R, STATA, and SPSS

Statistical analyses were performed in R, STATA, and SPSS to analyze the simulated data in the CTCD. All analysis scripts can be found in the Github repository *(https://github.com/bmagonggrijp/CTCD-Implementation-and-Methodological-Considerations).* The results from the analyses conducted in R, STATA, and SPSS are consistent, as shown in Supplementary Tables 2.2, 2.3, and 2.4, respectively. We again note that the estimation of associations in the twin analyses relies on discordant twin pairs contributing to the within-pair association's estimation. Consequently, not all twin pairs are included when, for example, a conditional logistic regression is performed, and thus the exact number of contributing twins should be carefully checked and reported in publications. Among the software packages we worked with, STATA and R provided this information in the results. In SPSS, conducting a conditional logistic regression requires specifying that only discordant twins should be selected for analysis to obtain the correct within-pair estimate for fixed effects and conditional logistic regression. The analyses of the simulated data demonstrate that if these steps are performed correctly, the three software packages produce exactly the same regression coefficients, with slightly different confidence intervals in SPSS compared to those in R and STATA.

Figure 2.2 presents the results of the different simulation analyses for each scenario depicted in Figure 2.1. The analyses vary depending on the type of variables involved

(continuous or binary) and reveal differences in the magnitude of the association within the same scenario. In the top part of Figure 2.2, scenario A is depicted, where no confounding is present. The simulation analyses of continuous exposure and outcome variables show an expected pattern with consistent association magnitudes across the population sample and both DZ and MZ discordant twin analyses. However, when examining binary variables, there is a slight deviation from the expected pattern, due to the introduction of variability when deriving binary variables from continuous variables during the simulation process.

The second part of Figure 2.2 illustrates scenario B, where only genetic confounding is present. In each analysis, for both continuous and binary variables, an association is observed in the population sample, while there is no association in the MZ discordant twins, and the DZ twins show an intermediate pattern. The third part of Figure 2.2 shows the simulation of scenario C, which involves confounding by shared environmental factors. As expected, only the population sample shows an association, while the association within the twins is either zero or not significantly different from zero. The association in the population sample is relatively small compared to the other scenarios because the simulated exposure and outcome variables both had a relatively low contribution of shared environmental factors (0.22 and 0.10, respectively).

Finally, the fourth part of Figure 2.2 depicts a scenario where there is partly genetic and shared environmental confounding. Here again, the expected patterns emerge, with reduced association magnitudes within DZ and MZ pairs compared to the effect within the population sample. Thus, under the assumption of no unshared environmental confounding, we draw correct conclusions with respect to the presence or absence of genetic or shared environmental confounding.

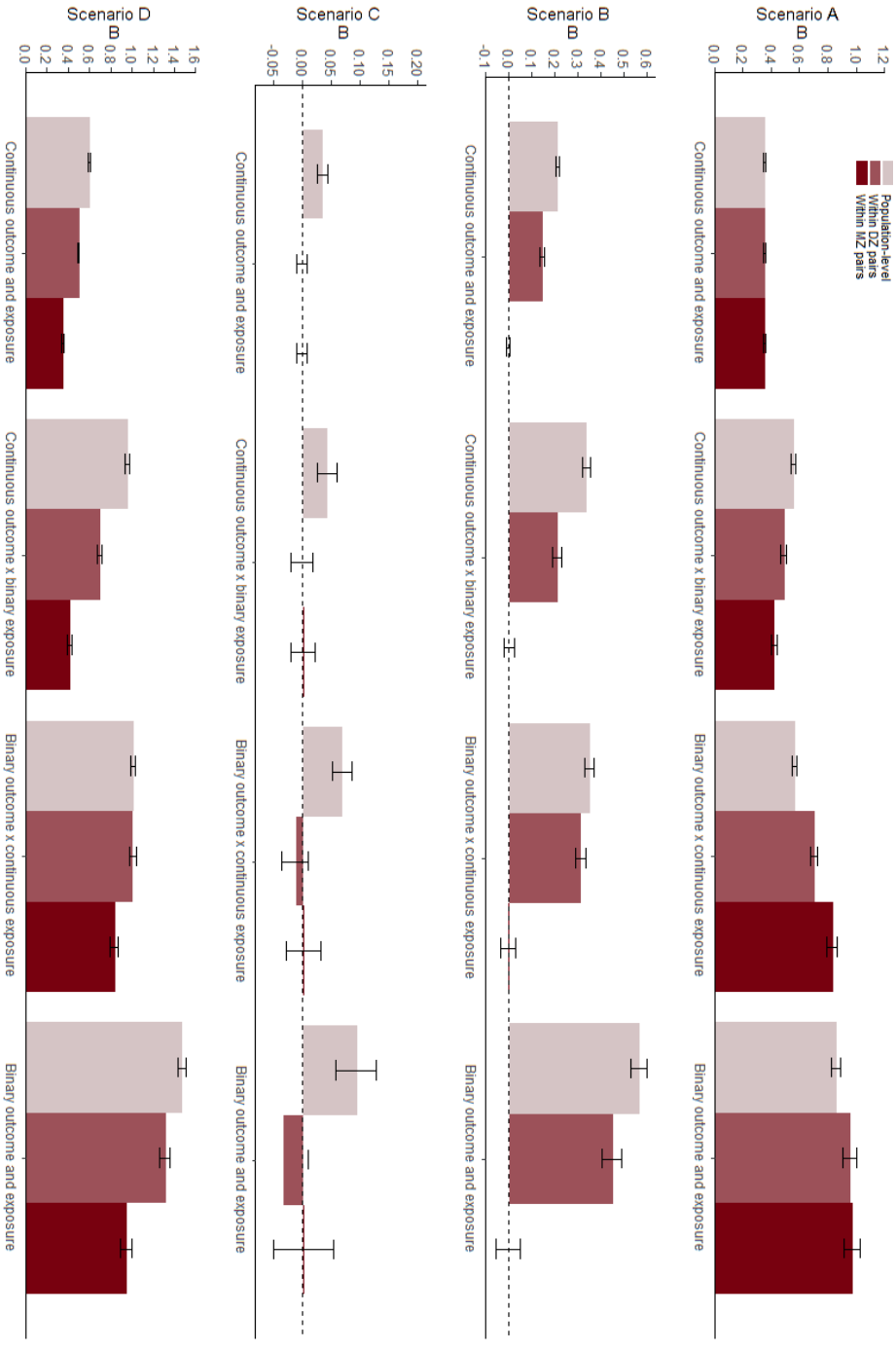

Fig. 2.2. Results from simulation analyses, depicting the relationship between exposure and outcome at the population level, and within discordant dizygotic (DZ) and monozygotic (MZ) twins under different scenarios and types of variables. B = regression coefficient. Scenarios A = no confounding, B = solely genetic confounding, C = solely shared environmental confounding) and D = Causal effect with genetic and shared environmental confounding.

Discussion

The Co-twin control design (CTCD) is a valuable tool for investigating causal associations while controlling for confounding by shared environmental and genetic factors. In this paper, we reviewed common analysis methods for CTCD with binary or continuous outcome and exposure variables and provided practical guidance and scripts for implementing the design in R, SPSS, and Stata, and illustrating them using simulated data. The CTCD's greatest strength lies in its ability to control for unmeasured genetic and shared environmental factors, providing evidence for a causal association. However, the CTCD cannot completely rule out alternative explanations for observed associations.

One assumption in the CTCD is the absence of confounding by non-shared environmental factors. While MZ twins share genetic and some environmental influences, they also have non-shared experiences and exposures that make them unique. Consequently, when the association of exposure with the outcome within the population sample is similar to the within-DZ and within-MZ pairs association this may reflect true causality, but it can also reflect the effect of the nonshared experiences that led to differences in exposure.

Secondly, the CTCD cannot distinguish between causation and reverse causation (McGue, Osler, & Christensen, 2010). Causation refers to the traditional understanding that variable X causes variable Y, while reverse causation means that Y causes X. The CTCD is designed to test for a possible causal association based on prior theory about the cause and the consequence, which could be the case for example when a causal variable was measure before the outcome variable. Analyzing data from longitudinal twin studies can help rule out possible reverse causation. Within twin research, several approaches have been developed to explore the direction of causation, such as the direction of causation model (DCM) (Gillespie & Martin, 2005; Heath et al., 1993). The DCM is designed to address the direction of causality when two variables have different genetic architectures, such as an AE versus a CE model.

The CTCD, and other causal designs, may fail to detect a within-pair association due to measurement error. According to classical test score theory, the presence of

measurement error in the exposure variable has a more pronounced impact on within-pair associations compared to individual-level associations due to the compounded effect of error inherent in calculating difference scores (Ashenfelter & Krueger, 1994). To illustrate, consider the interplay between σ, an estimate of the proportion of measurement error in the exposure variable, and ρ, the twin correlation. At the individual level, the regression coefficient of the outcome on the exposure is attenuated by σ. However, at the within-pair level, the attenuation is influenced by σ/(1−ρ) (Frisell et al., 2012; McGue, Osler, & Christensen, 2010). Consequently, when measurement error accounts for, for example, 5% of the exposure variable, the individual-level estimate would be attenuated by 5%. However, the within-pair estimate would be attenuated by 25% when the twin correlation on exposure is 0.8 and by 12,5% when the twin correlation is 0.6. Measurement error thus leads to a greater attenuation in the DZ and MZ analyses, compared to the association at the population level. Moreover, as MZ twin correlations are typically higher than DZ twin correlations, it is expected that the within-pair attenuation will be greater for MZ than for DZ pairs. Frisell et al. (2012) conducted a series of simulations in paired sibling data under a logistic model with binary exposure and outcome, where the association of x and y was causal and not confounded. Their simulations demonstrated measurement error to lead to an attenuation of the unpaired OR estimates and to an ever greater attenuation of the within sibling OR. That is, measurement error in the exposure variable can result in the underestimation of causal effects or the failure to observe significant within-pair associations, even when a causal association is present between the exposure and outcome (Duffy & Martin, 1994; Frisell et al., 2012; McGue, Osler, & Christensen, 2010).

The CTCD may also fail to detect a within-pair association due to a "spill-over" effect. This effect occurs when the exposure being investigated not only affects the exposed twin but also influences the non-exposed twin within the pair. The likelihood of observing a spill-over effect varies depending on the nature of the exposure. For example, research has shown that certain exposures, such as victimization of sexual abuse within a family, can impact not only the victimized individual but also non-victimized family members (de

Jong, 2022). In contrast, exposures like birth weight are highly unlikely to exert an influence on the co-twin.

In this paper, we provided an overview of the CTCD with a focus on its application to data from large twin registries. However, this is not always feasible when, for example, studying rare outcomes or exposures. In such cases, researchers may face challenges in obtaining a sufficient sample size of discordant MZ twin pairs. For such rare diseases and disorders, the ascertainment into a research project may be through other routes, such as patient registries.

In conclusion, the CTCD can be a powerful design for investigating causal associations while controlling for genetic and shared environmental confounding factors. This article aids future researchers to employ the CTCD by presenting an overview and discussion of its strengths and limitations. By providing a set of scripts that can be readily used with the popular statistical software packages SPSS, R, and STATA, and by providing tools to aid in data simulation, we aimed to contribute to an understanding and application of the design.

Chapter 3.

Exploring the Relationships of Crime Victimization with Depression, Anxiety, and Loneliness in Twin Families

Abstract

Crime victimization is associated with a more unfavorable health profile. We examined associations of victimization of property, violent, and sexual crime with mental health indices for depression, anxiety, and loneliness and explore their etiology in Dutch twin families. The data were collected from adult twins, their parents, siblings, spouses, and offspring participating in longitudinal survey studies of the Netherlands Twin Register (N = 19,867). First, we tested if there is an association between victimization and loneliness, anxiety and depression at the population level. Second, discordant twin pairs were identified, where one twin was a crime victim and the cotwin was not. This design allows controlling for confounding by shared environment and genetic factors. Third, a longitudinal comparison was made of pre- and post-victimization data in victims, their family members, and unrelated individuals. At the population level, victimization was associated with increased depression, anxiety, and loneliness, except for property crime which was not associated with depression and anxiety. The associations were strongest for violent and sexual crimes. Within discordant twin pairs, no significant differences were found between the victimized and non-victimized twins. These results confirm that crime victimization is associated with adverse mental health outcomes and loneliness, with the strength of this association differing per type of crime. There is no strong evidence that the relationship between victimization and mental health or loneliness follows a simple causal model as the relationship can be partly explained by genetic and shared environmental confounding. These results also suggest that victims of sexual and violent crimes may already experience more mental health problems before victimization than non-victims and that individuals with more mental health problems and loneliness are at increased risk of becoming a victim.

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Exploring the Relationships of Crime Victimization with Depression, Anxiety, and Loneliness in Twin Families

Crime is a prevalent societal problem and is reported to have a significant impact on the well-being and health of victims. In 2021, 17.1 percent of the population in the Netherlands, the country on which the current study focuses, became a victim of one or more crimes. This comprised violent crimes (4.1%), sexual crimes (1.1%), property crimes (9.0%), or vandalism (6.0%) (Statistics Netherlands, 2022). Victimization has been associated with less favorable outcomes across multiple life domains, such as relationship formation, employment, criminal offending, and a wide range of mental health outcomes (Beckley et al., 2018; de Jong, 2022; Dworkin et al., 2017; Hanson et al., 2010; Jennings, Piquero, & Reingle, 2012; Krumm et al., 2018; Maniglio, 2009; Swanberg & Logan, 2005). Victims of crime also have an elevated risk for a wide range of adverse physical health outcomes and this has been linked to poor functioning of the brain and nervous system, cardiovascular-, gastrointestinal-, musculoskeletal-, reproductive, immune, and endocrine systems (Breiding, Black, & Ryan, 2008; Britt, 2001; Chrisler & Ferguson, 2006; Coker et al., 2000; Kramer, Lorenzon, & Mueller, 2004; Murray-Close et al., 2014).

Research on victimization and mental health problems has often focused on childhood or adolescent victimization and often only one type of victimization is included (e.g. only sexual victimization or violent victimization). Becoming a victim during childhood or adolescence, both sensitive developmental periods, is associated with an increased likelihood of various negative outcomes such as depression, anxiety, loneliness, and post-traumatic stress disorder (PTSD) (Boney-McCoy & Finkelhor, 1995; De Venter, Demyttenaere, & Bruffaerts, 2013; Jackson & Deye, 2015; Kilpatrick & Acierno, 2003; Kimmel, 2014; McKay et al., 2021; Turner, Finkelhor, & Ormrod, 2006). In addition, it can lead to several negative outcomes in adulthood such as bipolar disorder, substance abuse, decrease in self-esteem, anxiety, and depression (Isaacs, Hodges, & Salmivalli, 2008; Macmillan, 2001; Turanovic & Pratt, 2015). It is however important to note that previous life-course criminological literature suggests that victimization profiles are

heterogeneous over time (DeCamp & Zaykowski, 2015; Kong & Easton, 2019; Tillyer, 2014). Semenza, Testa and Turanovic (2021) for example found that individuals who were violently victimized during the transition to adulthood showed the most mental and physical health problems. Research based on adult violent victimization has been more limited and has often focused on specific types of crimes (i.e., domestic violence, sexual crimes, or property crimes). Still, previous research has found that adult victimization, including violent, sexual, and property crime, correlates with numerous psychological and mental health problems (Britt, 2001; Campbell & Wasco, 2005; Kimmel, 2014; Krahé & Berger, 2017; Kunst & Koster, 2017; Ruback & Thompson, 2001). For example, Choudhary, Smith and Bossarte (2012) examined the association of sexual violence victimization with depression and anxiety symptoms. Of the victims of sexual violence 18.82% reported being diagnosed with depression, 8.37% reported an anxiety disorder, and 28.28% reported being diagnosed with both depression and disorder. This was significantly higher compared to the non-victims (respectively, 7.39%, 3.75%, and 6%). Porcerelli et al. (2003) found, in a cross-sectional study of 1,024 family practice patients, that the women and men who were a victim of violence showed more depressive symptoms compared to non-victims.

While the results of these studies reveal an association between victimization and mental health, the question is whether victimization causes mental health problems, as confounding could be present. Confounding may arise when third factors influence both the risk of victimization and mental health issues. One specific type of confounding is genetic confounding which occurs when genetic factors influence both the risk of victimization and outcomes such as mental health problems. It has been established that mental health problems are influenced by genetic factors. Genetic contributions to variation in anxiety were estimated at 45% (Lamb et al., 2010) and roughly 30 to 50% for depression (Boomsma et al., 2000; Kendler et al., 2018; Polderman et al., 2015; Sullivan, Neale, & Kendler, 2000). Even though victimization might seem a chance occurrence, it does not happen at random and heritable traits have been identified that are associated with an increased risk of victimization (Beckley et al., 2018; Veldkamp et al., 2019). For example, Beaver et al. (2009) found that violent victimization in adults is heritable, and

chronic victimization has an even higher estimate of heritability. It is crucial to emphasize that when we describe victimization as heritable, we are not implying that there are specific genes that directly cause people to victimize others, but that research suggests that genetic factors influence an individual's characteristics (such as behavior or personality traits) that increase their chance of victimization. Previous research showed evidence of a shared genetic vulnerability for victimization and mental health problems, such as anxiety (Guimond et al., 2015), paranoid symptoms (Shakoor et al., 2015), and MDD (Kavish, Connolly, & Boutwell, 2019).

One approach to studying the etiology of an association between exposure and an outcome, such as victimization and mental health problems, is by within-family designs (McGue, Osler, & Christensen, 2010). When siblings or twins within a family are discordant for the exposure, their degree of discordance for the outcome can inform on different mechanisms underlying the association. Twins and siblings share all, or part of, their genetic makeup. Monozygotic twins (MZ) share 100% of their genes, whereas dizygotic twins (DZ) and non-twin siblings share on average 50% of their segregating genes. By making comparisons within twin pairs, we thus automatically control for genetic confounding, either partly (DZ twins) or completely (MZ twins). Siblings and twins also share many (familial) environmental exposures which for twins also include prenatal exposures. Therefore, by comparing twins we automatically control for a wide variety of possible confounding factors that have been found to be related to both victimization and mental health, such as age, sex, SES, and household income (Willitts, Benzeval, & Stansfeld, 2004), SES (Hastings & Hamberger, 1997; Straus & Gelles, 2017).

Figure 3.1 shows the expected patterns of analyses in a general population and discordant twins under different mechanisms of causality and confounding. If there is a causal pathway between victimization and mental health, analyses in all groups (i.e., population analysis, same-sex DZ twin pairs, and MZ twin pairs) are expected to reveal effect sizes larger than zero and they will be similar in all groups (left set of bars in Figure 1). Under the noncausal hypothesis where genetic factors completely explain the association (2nd set of bars in Figure 3.1), discordant MZ twins are expected to have an

effect size of zero because they are genetically identical and are thus exposed to the same genetic risk factors. The DZ twins show an intermediate pattern. If the model is only partially explained by genetic factors, we expect a similar pattern, but the effect size of the MZ twins will be above zero (3rd set of bars in Figure 3.1). Finally, if the association is noncausal but completely explained by shared environmental factors, all discordant twins are expected to have an effect size of zero (4th set of bars in Figure 3.1), as twins have been raised in the same family and in these analyses, we automatically control for all shared environmental factors (Lichtenstein et al., 2002; Slob et al., 2020). Studies of twin pairs discordant for victimization exposure have reported an increased risk of emotional or behavioral problems in the victimized twin (Arseneault et al., 2008; Connolly et al., 2022; Kendler et al., 2000; Silberg et al., 2016), while other studies reported little to no effect (Berenz et al., 2013; Bornovalova et al., 2013; Dinwiddie et al., 2000). It is important to note that these twin-based studies are difficult to compare as they often looked at different types of victimization and different mental health disorders in various populations at different ages. A substantial number of these discordant twin analyses have focused on child or adolescent victimization (Dinkler et al., 2017; Donahue et al., 2017; Kendler et al., 2000). Schaefer et al. (2018) analyzed 625 MZ and 491 DZ UK twin pairs discordant for the exposure to domestic violence between the mother and her partner, frequent bullying by peers, physical maltreatment by an adult, sexual abuse, emotional abuse, and neglect, or physical neglect. Results showed that both childhood and adolescent victimization increased the risk of mental health problems (such as depression, anxiety, PTSD, and substance abuse) independent of family background and genetic risk. In contrast, Dinwiddie et al. (2000) looked at childhood sexual abuse (CSA) and the prevalence of psychiatric disorders. In the full sample (N= 5,995 Australian twins) CSA was associated with major depression, conduct disorder, panic disorder, and alcoholism, and participants were more likely to report suicidal ideation and a history of a suicide attempt. However, no differences were found when comparisons were restricted to discordant twin pairs (N= 64 MZ and 112 DZ twin pairs).

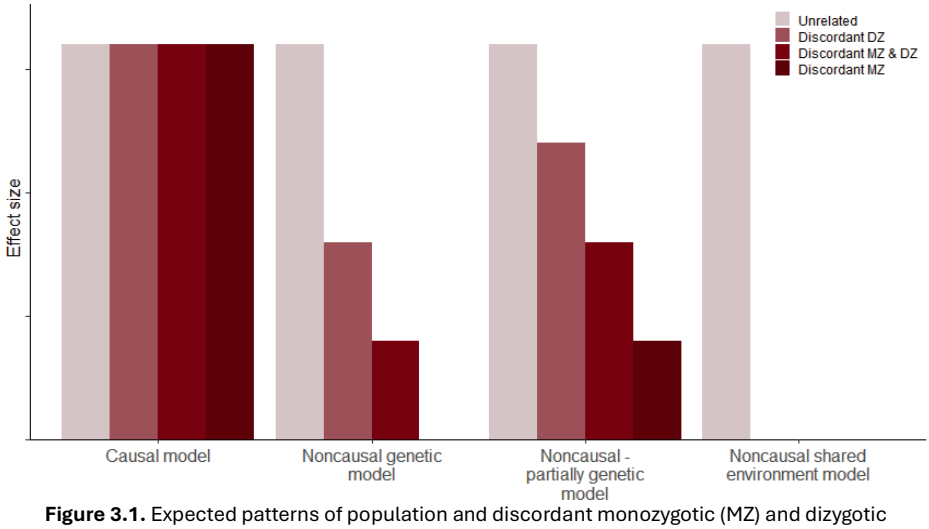

Figure 3.1. Expected patterns of population and discordant monozygotic (MZ) and dizygotic (DZ) twin analyses under the causal and non-causal hypothesis.

To the best of our knowledge, only one previous discordant twin-pair study has examined adult victimization and mental health (Connolly et al., 2022). They found that twins who experienced more intimate partner victimization reported more symptoms of depression than their co-twin (N = 471 American twin pairs). Because most discordant twin studies have concentrated on childhood or adolescent victimization, our knowledge regarding the impact of adult victimization over the life course of various crimes remains limited. It is often seen that siblings regularly share experiences of victimization in childhood, especially twins (Jaffee et al., 2004). Thus, with the limited number of discordant twins or siblings, it can be difficult to determine whether certain outcomes are caused by victimization using a discordant twin design in children or adolescents. In contrast, as twins age, they share fewer experiences and therefore also fewer experiences of victimization, making this analytical approach in adults more feasible.

The Current Study

In this study, we investigated the association between victimization, mental health problems, and loneliness in adults. We focused on depression, anxiety, and loneliness as outcome measures and look at three different types of victimization, namely violent, sexual, and property crimes. This enabled us to take into account possible heterogeneous associations with different types of crime, which may impact in different

ways on victims. We first compared victims and non-victims on these outcomes at a population level in a large sample of participants unselected for exposure or outcome. The participants are included in longitudinal survey studies and were assessed because they are twins or family members of twins. This offered the unique possibility to also apply a discordant twin design to address questions regarding confounding. Lastly, we investigated whether an association between victimization and mental health problems exists prior to victimization.

Methods

Participants

The data were collected from adult twins, their parents, siblings, spouses, and offspring who take part in studies with the Netherlands Twin Register (NTR). Recruitment of twins and their family members is via several routes, e.g. through city councils in the Netherlands, the yearly NTR newsletter Twinfo, the NTR website, and national events organized by, for example, the Dutch Twin Society. Twins who are registered by their parents after birth are invited to take part in self-report surveys after adolescence. Respondents fill out surveys on health and lifestyle every two to four years since 1991. Detailed information on the data collection procedures in the NTR, including the number of registered participants by role and age group and response rate have been reported in detail (Ligthart et al., 2019; Middeldorp et al., 2008; Vink & Boomsma, 2008; Vink et al., 2004) showing, for example, good representatives for data collected on health, personality, and lifestyle.

The present study is based on data from the four surveys, collected in 2000, 2002, 2004, and 2009, which asked about exposure to life events including crime victimization. The surveys from 2004 and 2009 assessed loneliness, the surveys from 2000 and 2002 assessed anxiety, and the surveys from 2000, 2004, and 2009 assessed depression. The data were combined across surveys to create the largest possible dataset for the three outcome measures. If participants filled out multiple surveys that contained the outcome variable of interest (e.g., 2000 and 2002 for anxiety) we selected the most recent survey for that specific variable and the victimization data from the same survey. If a

participant belonged to a twin pair, preference was given to the most recent survey to which both twins had responded (2.267 twin pairs within the same survey, 69.37%). The selection of participants for each different analysis is detailed in Figure 3.2.

Twin zygosity was determined by genotyping or by self- and parental reports concerning the physical resemblance of the twins or confusion by other family members and peers, showing excellent agreement (Ligthart et al., 2019). We selected all participants aged at least 25 years with complete data for victimization. The total sample consisted of N = 19,867 participants (see Table 3.1). Twins whose zygosity was unknown were excluded from the discordant twin analyses ($N_{loneliness}$ = 2, $N_{anxiety}$ = 2, $N_{depression}$ = 4). Data from participants who had filled in multiple surveys showed high consistency when looking at sexual or violent victimization; only 2.43% of the participants who reported sexual victimization did not report their sexual victimization again in later surveys, this was 3.20% for violent crimes. Reporting of property crime was more inconsistent with 12.67% of the participants who had reported property crime in an earlier survey, not reporting this in a later survey.

Table 3.1. Sample distribution for loneliness, anxiety, and depression analyses, and for the total sample combined.

	Twins	Siblings	Parents	Others*	Total	Males	Females
Loneliness	7,036	1,868	6,863	1,492	17,259	6,587	10,672
Anxiety	4,115	1,444	2,189	1,398	9,146	3,817	5,229
Depression	6,005	1,791	5,827	1,630	15,253	6,014	9,239
Total sample	4,118	6,005	2,322	7,422	19,867	7,899	11,967

* i.e., partners, offspring of twins

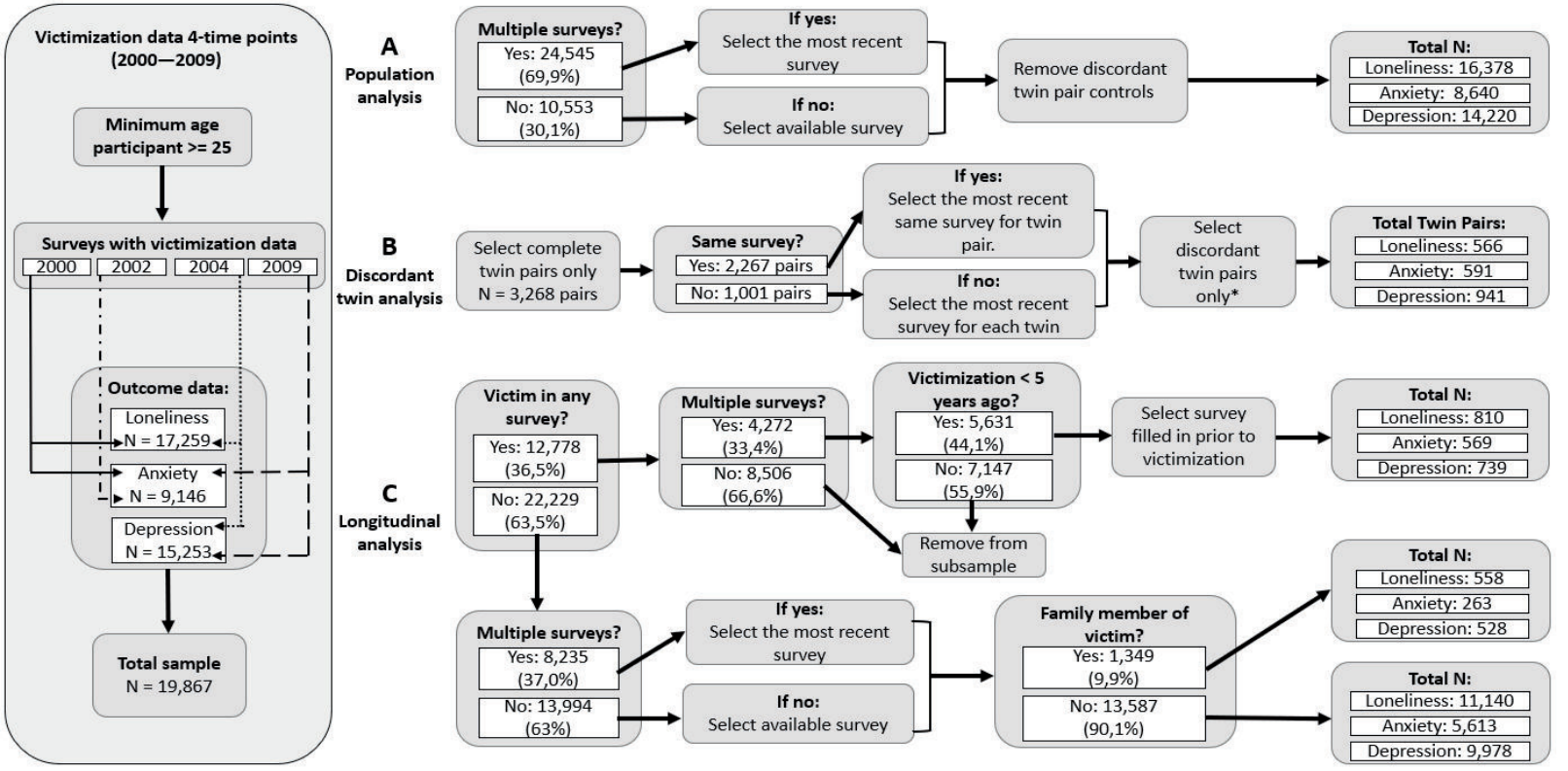

Figure 3.2. Flowchart of the selection procedure in each analysis. Each row (A – C) illustrates the available data and selection criteria for the particular analysis. * Both for same-sex DZ and MZ twins.

Exposure

Victimization

In all four surveys a Dutch life event scale (*the Schokverwerkings Inventarisatie Lijst*; Van der Velden et al., 1992) with a Cronbach's alpha of 0.73 was included. This scale asked: *'What events have happened to you in your life?'.* The scale includes a variety of life events, such as the death of a spouse, serious illness, or divorce. However, the present study focused on victimization and therefore included all the available victimization items, which were: property crime, (*theft, burglary, vandalism*), violent crime (*robbery, physical assault*), and sexual offense (*rape, sexual assault*). Response categories for the surveys in 2000 and 2002 were "*never experienced*", "*0–6 months ago*", "*6–12 months ago*", "*1–5 years ago*" and "*more than 5 years ago*". In the surveys in 2004 and 2009 the response categories did not include *"0–6 months ago*" and "*6–12 months ago*", but instead "less than a year ago" was used. To have uniform response categories across surveys the response categories from the surveys in 2000 and 2002, *"0–6 months ago*" and "*6–12 months ago*", were combined to "less than a year ago". When more than one victimization of the same type of crime was reported by a participant, we selected the most recently reported crime. Although considerable numbers of respondents indicated to have ever been victimized by any type of crime (victimization prevalence, see Table 3.2), the number of twins who had been victimized in each separate time frame was relatively small. Therefore, the original response categories that incorporated time of victimization were collapsed into a single binary variable (ever victimized yes/no) for both the population analysis and the discordant twin analyses.

Outcomes

Loneliness

Loneliness was measured in 2004 and 2009 with the Three-Item Loneliness Scale, which has a Cronbach's alpha of 0.81. Specifically, the items "*how often do you feel that you lack companionship?*", "*how often do you feel left out?*", "*how often do you feel isolated from others?*" were used. The items are rated on a 3-point scale: 1 = hardly ever; 2 = some of the time; 3 = often.

Anxiety

Trait-anxiety (i.e., the tendency to experience negative emotions across many situations; Gidron, 2013) was measured in 2000 and 2002 with the Spielberger Trait-Anxiety Inventory (STAI), which is a self-report questionnaire measuring how anxious people feel across situations on a daily basis (Boomsma et al., 2000). It comprises 20 items such as: "*I worry too much about something that really does not matter*", "*I am content*" and "*I am a steady person*". Participants can respond on a 4-point Likert scale ("*Almost never*", "Sometimes", "Often" and "*Almost always*") and some items are reverse-scored. The STAI has a Cronbach's alpha of 0.75.

Depression

Depression was measured by the Adult Self Report (ASR), which has a Cronbach's alpha of 0.91. In the ASR, participants report their behavior, thoughts, and feelings of the previous 6 months by rating how applicable the items are. Each item is rated from 0 = not true, 1 = somewhat true, to 2 = very true. Two example items are "*I feel confused or in a fog*" and "*I feel worthless or inferior*". The 2009 survey included all 18 items from the ASR scale. The 2000 survey included 17 items and the 2004 survey 15. Aseba (2023) shows all 18 items from the ASR scale.

IRT Scoring

All outcome variables were defined by Item-Response Theory (IRT; Embretson and Reise 2000) and calculated with the Generalized Partial Credit Model (GPCM) in R, with the *mirt* package (Chalmers, 2012). GPCM is an Item Response Theory model developed to analyze polytomous data. The benefit of an IRT score over a simple sum score is that it appropriately weights the relative contributions of individual items to a scale with a more favorable distribution, and takes into account missing data. Scores for each participant are relative to all other participants in that wave of data collection, as a separate model is fitted for each wave of data collection. Therefore, potential 'wave' or data collection effects are filtered out and the mean IRT score of each wave is zero.

Study Design and Analyses

To examine whether victimization was associated with loneliness, anxiety, and depression we proceeded in three steps (Lichtenstein et al., 2002). First, a population analysis was conducted to assess if there is an association between victimization and loneliness, anxiety and depression at the population level. All family members were included except for the controls from the discordant twin pairs (i.e., non-victimized twin; controls removed; $N_{loneliness}$ = 1,066, $N_{anxiety}$ = 749, $N_{depression}$ = 941). See Figure 3.2A for an illustration of the data selection. For the population analysis, we used Generalized Estimating Equation (GEE) linear regression models to account for familial clustering, with victimization as the exposure and anxiety, loneliness, and depression as the outcome variables, controlling for age and sex. Analyses were performed in SPSS version 24.

Second, a co-twin matched analysis in all same-sex discordant twin pairs was performed. Twin pairs are discordant if one of them had ever been a victim of a crime and the other had not. This approach corrects for shared environment and for shared genetic variants, as data from dizygotic (DZ) and monozygotic (MZ) twin pairs were included in one analysis. Next, we conducted a matched co-twin analysis separately in DZ and MZ twin pairs discordant for victimization. In the MZ pairs, we now control for all shared genetic and environmental factors. See Figure 3.2B for an illustration of the data selection. Fixed effect regression analyses were conducted within twin pairs discordant for victimization in Stata statistical software, release 16 (Stata Corp, 2019).

To determine if an association between victimization and mental health already exists prior to victimization we conducted additional GEE analyses where pre- and post-victimization scores on loneliness, anxiety, and depression of victims were compared with non-victims. To look at both the pre- and post-victimization scores, only participants who had filled in multiple surveys could be included. If a participant indicated that their victimization had taken place more than 5 years ago, they were excluded from these longitudinal analyses, as we then could not determine when exactly victimization took place and if the available measurements of mental health or

loneliness were collected prior to the victimization. As a consequence, only information on mental health and loneliness was available after victimization occurred, and therefore we could not make a comparison between pre- and post-victimization for this specific group. If the victimization was 1 – 5 years ago or less than 1 year ago we would select the most recent data available prior to victimization. For the participants, who had not been a victim in any survey, all surveys could be included. If they filled out multiple surveys that contained the mental health questions of interest (e.g., 2000 and 2002 for anxiety) we selected the most recent survey for that specific mental health variable. See Figure 3.2C for an illustration of the data selection. The sample distribution for the longitudinal analyses can be found in Supplementary Table 3.1. It was not possible to examine the discordant twin pairs' mental health before victimization as the sample sizes for these data were very low. Therefore we compared victims to non-victims who were divided into two groups, namely: their family members (parents, brothers, sisters) and unrelated individuals.

To account for multiple testing, q-values were computed for all P-values using the false discovery rate (FDR) correction with the R package q-value. A q-value is an estimate of the proportion of false discoveries among all significant p-values (Benjamini & Hochberg, 1995). The q-value threshold for declaring significance was 0.05 (that is, the top 5% of the significant findings are, on average, allowed to be false discoveries).

Results

Descriptive Statistics

We first describe the prevalence of victimization, for all participants, as well as separately for twins, men, and women. Table 3.2 shows the frequencies of victimization in the entire sample and the descriptive statistics for loneliness, anxiety, depression, and age of the sample. The percentage of men who had been victimized by a violent crime (6.1%) or a property crime (24.2%) was higher than the percentages of women (respectively 3.7% and 21.1%). Women more often reported sexual assault victimization (7.5% against 0.8%). Loneliness, anxiety, and depression mean scores were higher for women than for men. Descriptive statistics were also obtained for each survey

separately (see Supplementary Table 3.1). Overall, the mean scores of the outcome variables were comparable for the different surveys. The mean age, percentage of men and women, and victimization rates differed somewhat between the surveys as participants age over time and the invitation policy of the NTR was not always the same, but no major differences were found between the surveys. Looking at the differences between twins and non-twins, Table 3.2 indicates that victimization rates, as well as mean scores on loneliness, anxiety, and depression, are similar to non-twins. To test for significance, twin singletons were compared to their singleton siblings. No significant differences were found for loneliness (t(211) -0.668, q= 0.505), anxiety (t(689) 1.064, q= 0.288), and depression (t(143)= -0.029, q= 0.977), nor for any of the victimization variables (violent crime (X^2(5, N=1243)= 1.531, q= 0.909), sexual crime (X^2(4, N=1243) = 2.596, q=0.627) and property crime (X^2(6, N=1258)=9.164, q=0.165)).

Table 3.3. shows the discordance and concordance rates for the victimization of twins split by sex and zygosity group. The concordance (both twins victimized) rates for sexual and violent crime are higher for MZ twins than for DZ twins. The same was found when looking at property crime in the female twins. However, in the male twins, the concordance rate for property crime was higher in the DZ twins compared to the MZ twins, which suggests that genetic factors have a limited influence on property crime victimization.

Table 3.2. Descriptive statistics of ever being victimized, mean age and mean IRT scores for loneliness, anxiety, and depression of the overall sample.

	All		Men		Women		Twins		Non-Twins	
	Yes (%)	**No (%)**	**Yes (%)**	**No (%)**	**Yes (%)**	**No (%)**	**Yes (%)**	**No (%)**	**Yes (%)**	**No (%)**
Violent crime	4.6	95.4	6.1	93.9	3.7	96.3	4.3	95.7	4.3	95.7
Sexual crime	4.9	95.1	0.8	99.2	7.5	92.5	4.6	95.4	4.7	95.3
Property crime	22.3	77.7	24.2	75.8	21.1	78.9	25.7	74.3	25.8	74.2
	Mean (Min-Max)	**SD**	**Mean (Min-Max)**	**SD**	**Mean (Min-Max)**	**SD**	**Mean (Min-Max)**	**SD**	**Mean (Min-Max)**	**SD**
Loneliness	-0.023 (-0.73 - 2.67)	.789	-0.132 (-0.73 - 2.67)	-0.738	.044 (-0.73 - 2.67)	.813	0.008 (-0.73 - 2.67)	0.804	-0.045 (-0.73 - 2.67)	0.778
Anxiety	-0.029 (-2.19 - 3.75)	.962	-0.195 (-2.19 - 3.10)	.941	.094 (-2.19 - 3.75)	.959	-0.019 (-2.19 - 3.75)	0.981	-0.071 (-2.19 - 2.81)	0.945
Depression	-0.066 (-1.57 - 3.84)	.803	-0.312 (-1.57 - 3.84)	.854	.094 (-1.57 - 3.84)	.895	-0.011 (-1.57 - 3.84)	0.926	-0.104 (-1.57 - 3.36)	0.877
Age	46.01 (25 - 97)	12.68	48.81 (25 - 89)	12.976	46.01 (25 - 97)	12.383	41.63 (25 -97)	12.339	50.88 (25 - 91)	11.459

Table 3.3. Number and percentages of discordant and concordant twin pairs for violent, sexual, and property crime victimization on data from MZ and DZ complete twin pairs, divided per outcome variable.

	Violent crime						Sexual crime						Property crime					
	Concordant no victimization		Discordant		Concordant victimization		Concordant no victimization		Discordant		Concordant victimization		Concordant no victimization		Discordant		Concordant victimization	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Monozygotic Male Twin Pairs																		
Loneliness	311	84%	48	13%	10	3%	361	98%	7	2%	1	0%	161	44%	148	40%	60	16%
Anxiety	167	85%	25	13%	4	2%	194	99%	1	1%	1	1%	105	54%	73	37%	18	9%
Depression	253	84%	42	14%	7	2%	296	98%	6	2%	0	0%	139	46%	117	39%	46	15%
Monozygotic Female Twin Pairs																		
Loneliness	934	88%	112	11%	13	1%	896	85%	130	12%	33	3%	555	52%	374	35%	130	12%
Anxiety	525	89%	53	9%	10	2%	481	82%	89	15%	18	3%	293	50%	226	38%	69	12%
Depression	765	88%	96	11%	12	1%	719	82%	127	15%	27	3%	448	51%	322	37%	103	12%
Dizygotic Male Twin Pairs																		
Loneliness	135	78%	18	10%	20	12%	169	98%	3	2%	1	1%	89	51%	54	31%	30	17%
Anxiety	96	91%	8	8%	2	2%	102	96%	4	4%	0	0%	47	44%	44	42%	15	14%
Depression	116	87%	15	11%	2	2%	128	96%	5	4%	0	0%	66	50%	44	33%	23	17%
Dizygotic Female Twin Pairs																		
Loneliness	402	90%	42	9%	5	1%	369	82%	72	16%	8	2%	221	49%	192	43%	36	8%
Anxiety	255	89%	26	9%	5	2%	247	86%	34	12%	5	2%	162	57%	101	35%	23	8%
Depression	347	90%	33	9%	5	1%	320	83%	59	15%	6	2%	188	49%	166	43%	31	8%
Dizygotic Opposite Sex Twin Pairs																		
Loneliness	359	87%	51	12%	2	0%	366	89%	45	11%	1	0%	220	53%	150	36%	42	10%
Anxiety	236	86%	30	11%	7	3%	248	91%	23	8%	2	1%	152	56%	101	37%	20	7%
Depression	309	87%	45	13%	3	1%	318	89%	35	10%	4	1%	182	51%	138	39%	37	10%
All Twins																		
Loneliness	2141	87%	271	11%	50	2%	2161	88%	257	10%	44	2%	1246	51%	918	37%	298	12%
Anxiety	1279	88%	142	10%	28	2%	1272	88%	151	10%	26	2%	759	52%	545	38%	145	10%
Depression	1790	87%	231	11%	29	1%	1781	87%	232	11%	37	2%	1023	50%	787	38%	240	12%

Figure 3.3 shows the mean IRT scores of loneliness, anxiety, and depression separately for victims and non-victims. Higher mean scores of loneliness, anxiety, and depression were found for victims compared to non-victims. Differences were most pronounced for victims of sexual and violent crimes. Looking at loneliness, the highest mean score was found for sexual crime victims more than 5 years ago ($mean_{loneliness}$ 0.354, SD 0.957). For anxiety and depression, the highest mean scores were seen for victims of a sexual crime 1 - 5 years ago ($mean_{anxiety}$ 0.486, SD 1.18; $mean_{depression}$ 0.456, SD 1.061).

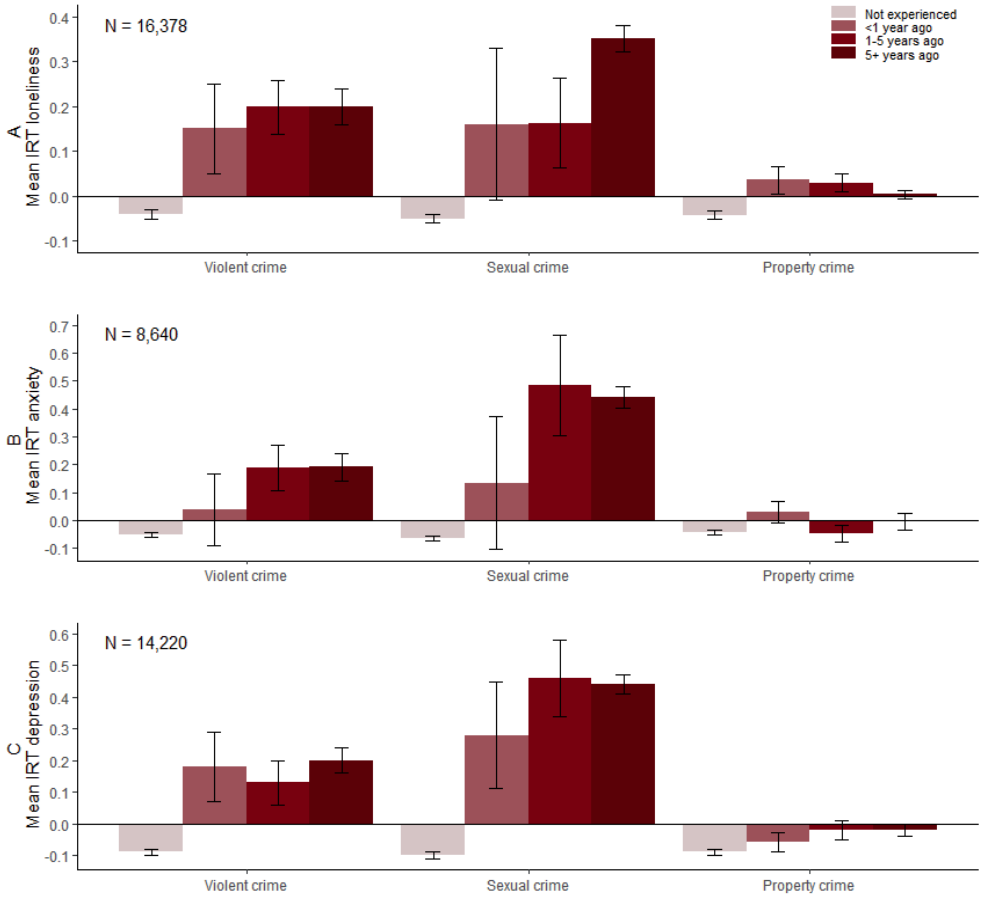

Figure 3.3. Mean IRT scores of loneliness (A), anxiety (B) and, depression (C) for non-victims and victims of violent, sexual and, property crimes.

Results from the population analysis are given in Table 3.4. The population analyses showed significant positive associations between loneliness and victimization of a sexual crime (B= 0.294, q<.001), a violent crime (B= 0.203, q<.001), and property crime (B= 0.04, q=.004). The population analyses also showed significant associations between victimization of a sexual or violent crime and higher scores on anxiety (B= 0.345, q<.001 and B= 0.205, q<.001, respectively). Similarly, victimization of a violent (B= 0.372, q< .001) and sexual crime (B= 0.238, q<.001) were significantly related to depression. Victimization of property crime was not significantly associated with anxiety (B=0.008; q=0.885) or depression scores (B=0.035; q= .064). A clear effect for sex was found for all mental health variables: women had higher scores on loneliness (B= 0.153, q< .001), anxiety (B= 0.255, q<.001), and depression (B= 0.366, q<.001) compared to men. Lastly, a small age effect was found as older respondents had lower scores of depression (B= -0.002, q=.002). No age effects were found for experiencing loneliness or anxiety.

Results from the analyses with victimization split by the period of occurrence (i.e. less than 1 year ago, 1-5 years ago, longer than 5 years ago) can be found in Supplementary Table 3.2. The analyses presented in Table 3.4 were repeated for each survey. The results from these additional analyses generally showed associations in the same direction as presented in Table 3.4. (see Supplementary Table 3.3).

Discordant Twin Analyses

Figure 3.4. summarizes the results from the population analyses and the discordant twin pair analyses for loneliness, anxiety, and depression. The full results of the discordant twin analyses as well as the exact sample sizes can be found in Supplementary Table 3.4. W hile we found significant results in the population analyses, none of the discordant twin pair analyses indicated significant differences between victims and non-victims within pairs, suggesting that the association between victimization and mental health is confounded by genetic and/or shared environmental risk factors.

Table 3.4. Population analyses showing the association between victimization and loneliness, anxiety, and depression.

	Loneliness			Anxiety			Depression		
	B	**95% CI LL - UL**	**q**	**B**	**95% CI LL - UL**	**q**	**B**	**95% CI LL - UL**	**q**
Violent crime	0.294	0.233 - 0.355	<0.001	0.345	0.250 - 0.442	<0.001	0.372	0.302 - 0.441	<0.001
Sexual crime	0.203	0.142 - 0.263	<0.001	0.204	0.117 - 0.292	<0.001	0.238	0.17 - 0.306	<0.001
Property crime	0.04	0.013 - 0.067	0.004	0.08	-0.038 -0.054	0.801	0.035	0.003 - 0.067	0.063
Sex (ref = male)	0.153	0.129 - 0.177	<0.001	0.255	0.215 - 0.296	<0.001	0.366	0.338 - 0.395	<0.001
Age (years)	0.001	0 - 0.002	0.301	-0.001	-0.003 - 0	0.138	-0.002	-0.003 - -0.001	0.002

B = unstandardized regression coefficient, 95% CI = 95% confidence interval, LL = lower limit, UL = upper limit, q = FDR q-value, loneliness N = 16,378, anxiety N = 8,640 and depression N = 14,220.

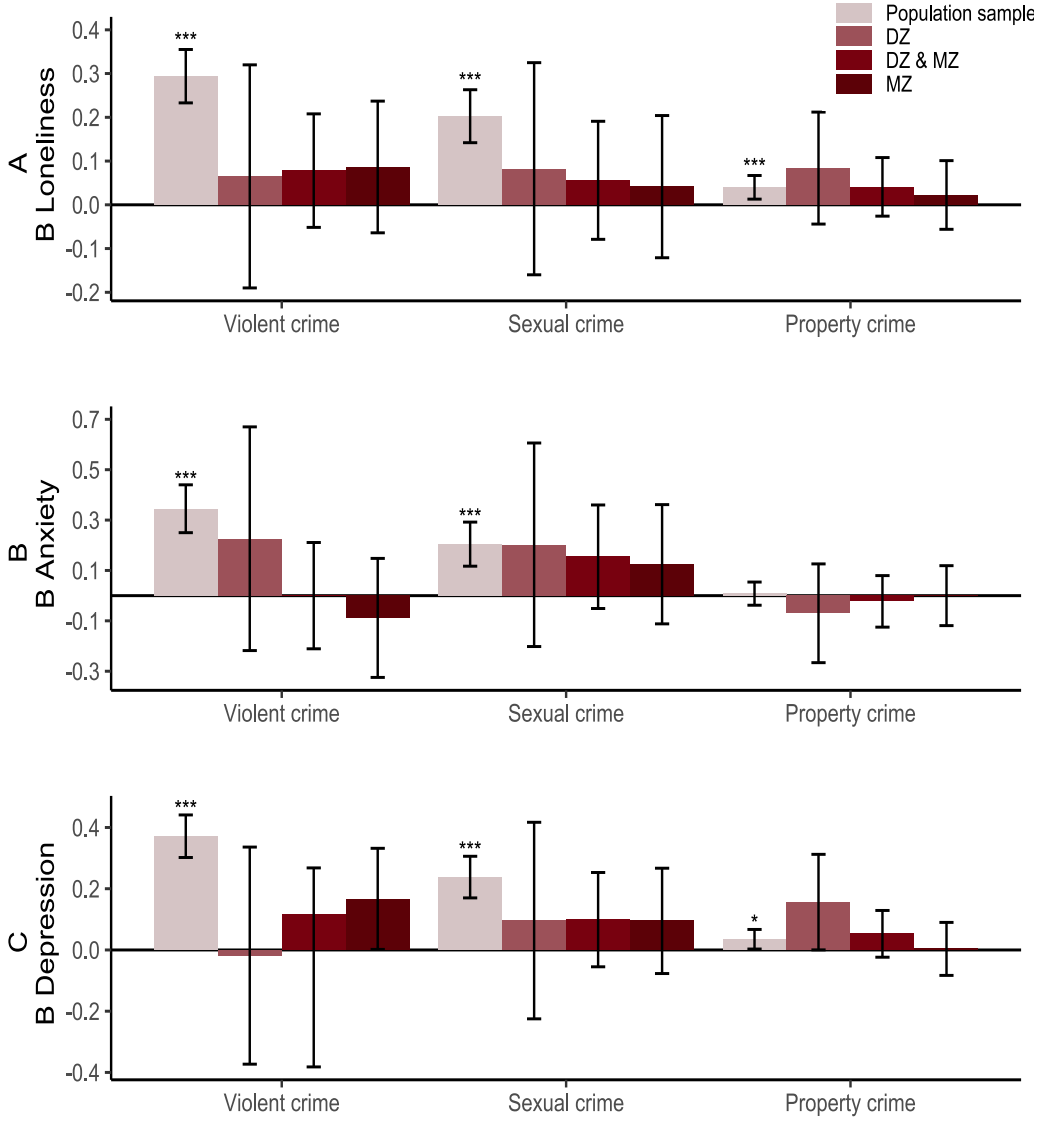

Figure 3.4. Comparison between the population analyses and analyses in the same-sex discordant twin pairs for loneliness (A), anxiety (B) and depression (C), separately for violent, sexual and property crimes.

Mental Health Prior to Victimization

To determine if an association between victimization and mental health existed prior to victimization, we compared the pre- and post-victimization scores between victims and non-victims (both related and unrelated to the victim). The mean scores on loneliness, anxiety, and depression prior to and after victimization is summarized for victims, their family members, and unrelated controls in Figure 3.5. Unrelated controls had significantly lower scores on loneliness compared to victims of sexual crime prior to victimization and violent crime victims prior to their victimization (B = -0.724, q= .015 and B= -0.296, q= .015, respectively). Victims of property crime showed no significant associations between depression, anxiety, and property crime prior to the victimization, but unrelated controls did have lower scores on loneliness when compared to the victims of property crime after victimization (B = -0.087, q= .023). Lastly, associations between related and unrelated control groups were tested. No significant differences were found, with the exception of the related control group for sexual crime reporting higher scores on depression compared to the unrelated control group (B= 0.340, q= .021). Supplementary Table 3.5. gives the mean scores and results from the population analyses of loneliness, anxiety, and depression pre- and post-victimization.

Looking at the overall trend of the mean scores pre- and post-victimization, victims showed a higher mean score on mental health both pre- and post-victimization compared to the non-victims irrespective of the type of victimization. The victims of sexual and violent crimes are closer in scores to their non-victimized family members, who consistently score lower than the victims, but higher than the unrelated controls. Victims of property crime on average score slightly higher than the non-victims, but are not always closer in scores to their family members. Interestingly enough, there also seems to be a decrease in experiencing anxiety, depression, and loneliness post-victimization, however, this decrease was not significant. These results indicate clearly that there are genetic and shared environmental factors that confound the association between (sexual and violent) victimization and mental health.

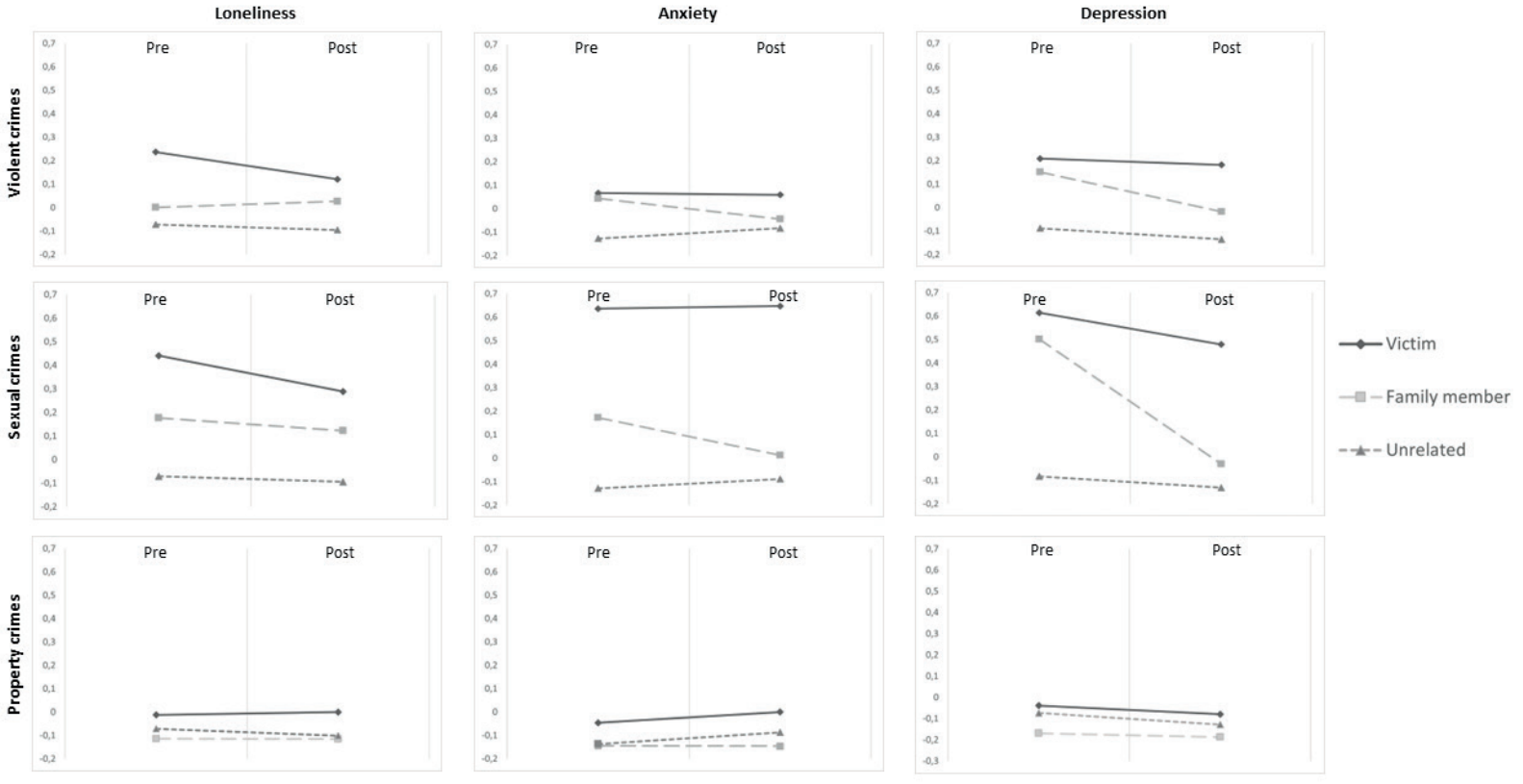

Figure 4.5. Average IRT scores on loneliness (left), anxiety (middle) and depression (right) pre- and post-victimization for violent, sexual and property crime victims compared to related and unrelated controls.

Discussion

This study aimed to investigate the association of victimization of various types of crime with loneliness, anxiety, and depression, using a population analysis and discordant twin design. We found clear associations in the population analyses between victimization and experiencing loneliness, anxiety, and depression. These findings were in line with previous research, that showed a correlation between victimization and mental health problems (Britt, 2001; Campbell & Wasco, 2005; Kunst & Koster, 2017). Our results furthermore indicated that women have a significantly higher chance of experiencing loneliness, anxiety, or depression compared to men, a finding also in line with previous research (Kessler, 2003; Zender & Olshansky, 2009).

Our study expressly distinguished between victimization of property, and violent and sexual crimes. This is an important contribution to the literature as research that compares the health consequences of various forms of victimization is sparse. Some focused on property crime specifically (Cook & Fox, 2011; Gale & Coupe, 2005; Kilpatrick et al., 1985), but the majority focuses on the consequences of specific forms of violent crime, such as sexual assault, and bullying or combined violent, sexual, and property crime victimization in one measure (Kilpatrick & Acierno, 2003; Morrall et al., 2010; van der Velden et al., 2021). Our findings underline the importance of disaggregating by type of crime, showing that the health effects varied by crime type. The analyses showed that victimization by violent and sexual crimes was clearly associated with more mental health problems and loneliness, as compared to property crime, with the association between property crime and mental health problems much weaker or even absent. As the current study focused only on anxiety, depression, and loneliness, future research is needed to focus on other types of mental health problems (i.e., PTST, sleeping disorders, and suicidality) to assess the scope of the impact of various types of criminal victimization.

The positive associations found in our population analyses do not necessarily imply causal effects. Discordant twin analyses were therefore conducted to investigate whether victimization and mental health in adulthood are confounded with shared

environmental and/or genetic factors. In discordant twin pair analyses, no differences were found between victims and non-victims, which shows that victims of property, violent or sexual crimes do not experience more mental health problems than their non-victimized twin. This finding is in line with most previous discordant twin studies of child victimization (Berenz et al., 2013; Bornovalova et al., 2013; Dinwiddie et al., 2000; Shakoor et al., 2015), with only one previous study finding that twins who experienced more intimate partner victimization reported more symptoms of depression than their co-twin (Connolly et al., 2022).

Several explanations can be put forward to explain our finding that a cross-sectional association between victimization and mental health was found, but no differences between victims and non-victims within families. The first of these is simply that victimization does not have a causal impact on mental health, and that the association at the population level is explained completely by confounding of shared environmental and genetic factors. This does appear counterintuitive and not in line with many victims' lived experiences.

A second possible explanation is in a sense the opposite of the previous one, as it posits that victimization has such a pervasive effect that not only the victimized person but also his or her twin is affected. This explanation has previously been coined as a 'spill-over' effect, i.e., when a family member is victimized, the victimization also affects non-victimized family members (de Jong, 2022). Our sample size did not permit us to study changes in the mental health of non-victimized twins from before to after victimization for the victimized twin. However, when comparing changes in mental health from before to after victimization for victims and their other family members, we found no evidence of a spill-over effect. Both victims and their family members showed no increase in mental health problems after the victimization had taken place.

Another explanation might be that offenders specifically target vulnerable victims. To investigate this, we also looked at mental health pre-victimization. Our results showed that victims already had higher scores on mental health problems before victimization, especially victims of sexual and, to a lesser extent, violent crimes. This finding is in line

with the extensive amount of previous research that has found patients with severe mental illness at substantially increased risk of victimization compared to other community members (Khalifeh et al., 2015; Krahé & Berger, 2017; Latalova, Kamaradova, & Prasko, 2014; Monahan et al., 2017; Rossa-Roccor, Schmid, & Steinert, 2020). For example, Middeldorp et al. (2008) found that adverse life events are associated with higher levels of anxious depression and scores on neuroticism. In turn, higher scores on neuroticism and anxious depression are associated with an elevated risk of exposure to adverse life events. Rossa-Roccor, Schmid and Steinert (2020) conducted a cross-sectional study and found an increased risk for theft, physical violence, and sexual harassment among people with severe mental illness. This finding concurs with rational choice and economic theory that posit that perpetrators will attempt to minimize their costs (amongst which risk of detection and punishment) by targeting vulnerable persons (Becker, 1968; Cornish & Clarke, 2017). The current study suggests that mental health problems symptoms may in fact be a warning sign for victimization risk, which could have important implications for clinical practice. To reduce victimization and its consequences effective prevention and intervention programs might more effectively target high-risk groups (i.e., those who experience mental health problems). In addition, as victims are a high-risk group for mental health issues, it is important that organizations that support victims pay attention to this in their assistance to the victims, regardless of whether these mental health issues are caused by the victimization or not.

Aside from the finding that victims had higher scores on mental health problems and loneliness before victimization, results also indicated that the victims resembled their non-victimized family members more than unrelated individuals. This finding is in line with the first explanation, the association between victimization and mental health problem can be explained by shared environmental and genetic factors, as it points to confounding familial factors that influence mental health as well as the risk of victimization. This is furthermore underscored by the result that most of the concordant (both twins have been a victim) rates for MZ twins were higher compared to the DZ twins when looking at sexual and violent crime, which suggests that these types of

victimization are also associated with genetic factors and that some people are simply more at risk of victimization than others.

Lastly, with regard to the discordant twin pair analyses, there can be important, but for statistical purposes small, differences between victims and non-victims that were not detected due to a lack of power. The current study employed a large dataset with over 17,000 participants, but the sample for the discordant twins was still relatively small, which could have led to the non-significant findings in the discordant twin analyses.

This study has several limitations that should be taken into account when interpreting the results. First, we analyzed self-report data from survey studies, and it is known that not all victims report victimization, for example, because they are ashamed of what happened to them, they do not remember their victimization, or they give socially desirable answers. Upon inspection, it turned out, however, that participants were fairly consistent in their self-report of sexual and violent victimization. Of the participants who filled out multiple surveys only 2.43% indicated that they had not been a victim of a sexual crime while they had reported being a victim in an earlier survey. For violent crimes, the inconsistency was 3.20%. However, for property crime, 12.67% of the participants gave conflicting answers. Possibly, many people might consider property crime to be a relatively regular event, which may lead to forgetting about the event in later surveys or not reporting it anymore because it has been forgotten, leading to inconsistency. Indeed, Averdijk and Elffers (2012) reported that when comparing results from a victimization questionnaire to police records, in 48% of the cases a respondent did not mention a victimization event that had been registered in police records. Such discrepancy might of course be due to how the survey question is interpreted, or because police reports have been filed wrongly, nevertheless it is clear that some events are simply not reported.

Second, our measures of victimization likely comprise a range of victimization events that vary in intensity (i.e., the theft of a bicycle versus a home burglary). If the less severe types of victimization are more common, this could mask the true effect of (more severe) victimization on mental health.

Third, we could not distinguish between participants who had been victimized multiple times (repeat victimization) and participants for whom the victimization was a single occurrence, nor do we know who the perpetrator was. Literature shows that victimization rarely occurs as a stand-alone and it is possible that the effect of repeat or poly-victimization is stronger in comparison to a single event (Finkelhor, Ormrod, & Turner, 2007). In addition, previous research found that the victim-offender relationship is important for the association between victimization and mental health problems. More symptoms regarding mental health problems are usually found if the offender was a known or trusted person (de Jong, 2022) or known to the victim (Demaris & Kaukinen, 2005; Lawyer et al., 2006). In this research, it was not known what the relationship between the victim and the offender was and thus we could not take this effect into account.

Fourth, although the current study focused on adult victimization, we cannot rule out that some victims were victimized in their childhood as participants could report that the crime had occurred more than 5 years ago, and it is likely that for some the victimization was during childhood or adolescence. Previous research found that the chances of becoming a victim, especially of violent crimes, are highest during childhood and adolescence and that victimization during these sensitive developmental periods can lead to mental health problems in adulthood (Macmillan, 2001). As the current research cannot completely rule out victimization during childhood and adolescence, we were unable to fully disentangle the effects of childhood or adolescent victimization from adult victimization.

Lastly, current research used the discordant twin design, a strong design in the sense that it controls for genetic and shared environmental confounders (and thus familial confounding). However, this design is not without limitations (Duffy & Martin, 1994; McGue, Osler, & Christensen, 2010). Firstly, even though the design corrects for shared environmental factors, non-shared environmental factors can still be present and influence the association. Measured non-shared environmental factors can be included as covariates, but many important non-shared environmental factors are difficult or not

possible to measure and thus these can still influence the association. Nevertheless, as basically all human behavior and traits are to some extent heritable (Polderman et al., 2015), we still expect to at least partly control for these non-shared environmental factors by comparing within twins. Second, the discordant twin design may fail to detect a within-pair association due to measurement error. It is expected that the within-pair attenuation will be greater for MZ than for DZ pairs. This may lead to the underestimation of causal effect or failure to observe significant within-pair association, even when there is a large enough sample and a causal association is present between the exposure and outcome (Duffy & Martin, 1994; McGue, Osler, & Christensen, 2010).

In conclusion, our results confirm associations between victimization and loneliness, and mental health problems. These associations differ depending on the type of crime, as it is stronger for violent and sexual crimes and much weaker for property crimes. Furthermore, we show that individuals who are more lonely, anxious, or depressed are at increased risk of victimization. Lastly, our discordant twin and longitudinal analyses indicated that the association is at least partly explained by genetic and shared environmental confounding, with some people seeming to be more at risk of becoming a victim than others. Future, particularly longitudinal or even life-span, research is essential to further examine the relationship between victimization and mental health and to better study additional explanations for our findings such as the proposed 'spill-over effect', and disaggregating by the seriousness of crime and relationship with the perpetrator. Gaining a better understanding of the relationship between victimization and mental health is not only important for theory but pivotal for policy and prevention.

Chapter4.

The Genetic Influence Of Social Support

Abstract

Social support is often considered an environmental factor affecting health, especially in aging populations. However, its genetic underpinnings suggest a more complex origin. This study investigates the heritability of social support through applying a threshold model on data of a large adult sample of twins (N=8,019) from the Netherlands Twin Register, collected between 2009 and 2011. The study employed the Duke – UNC Functional Social Support Questionnaire to assess social support quality. Our analysis revealed genetic contributions to social support, with heritability estimated at 37%, without a contribution of shared environment and no differences between men and women in heritability. The study's results underscore the complexity of social support as a trait influenced by genetic and environmental factors, challenging the notion that it is solely an environmental construct.

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The Genetic Influence of Social Support

Social support involves interactions with others, notably friends and family, creating an environment where individuals feel supported and appreciated (Taylor, 2011). It is often conceptualized as an environmental influence that mitigates the risk of physical and mental health conditions, especially in ageing populations (Plomin & Bergeman, 1991). Different societies exhibit varying levels of social support due to cultural values. For instance, collectivist cultures, like those in many Eastern societies, emphasize community and family ties, which often results in robust social support systems. In contrast, individualistic cultures, predominantly found in Western societies, encourage self-reliance, which might lead to less perceived social support (Taylor et al., 2007). As pointed out by Kendler (1997), however, viewing social support solely as an environmental measure may be incorrect. Agrawal et al. (2002) looked at perceived social support in a longitudinal study of female same-sex twin pairs, with ages ranging from 22 to 59 years from the Virginia Twin Registry. Heritability estimates ranged between 44% (relative support) and 75% (social integration) for six social support factors (i.e., friend support, relative support, friend problem, relative problem, confidants and social integration). A person's genotype thus seems to play a substantial role in creating and/or perceiving their social environment, possibly through genetically influenced traits such as cognition, temperament and personality.

Other research generalizes these findings to men. Agrawal et al. (2002) studied the same six factors in a sample of 7,506 male and female MZ and DZ twins and triplets with an average age of 36.6 years. While women had higher mean levels for most aspects of social support, there was no evidence for sex differences in the magnitude of genetic and environmental influences. In a more recent study, Coventry et al. (2021) looked at the Kessler perceived social support (KPSS) measure in 7,059 male, female and opposite-sex twin pairs aged 18-95 years from the Australian Twin Registry. There was some evidence for different genetic mechanisms in males and females for support from friends and the average KPSS score of all subscales, but otherwise, this study

confirmed there are few sex differences in the genetic architecture of indices of social support.

Wang et al. (2017) analyzed two indices of social support, namely support quality and support quantity, in 1,215 male and female 18-year-old twin pairs who take part in the Twins Early Development Study (TEDS). Both measures were heritable with estimates of 55% and 49%, respectively. Wang et al. (2017) suggested that these findings point to gene-environment correlation, where individuals create and perceive their supportive environment based upon their genotypes. Schnittker (2008) analyzed the heritability of social support and other traits related to success and happiness, in a sample from the National Survey of Midlife Development in the United States (MIDUS). The study included 3,023 unrelated individuals, 2,330 siblings, and 1,588 twins, aged 25–74 years. Genetic factors substantially influenced how individuals perceive and benefited from social support networks. Interestingly, there were quite large differences in heritability estimates, ranging from 26% and 22% for friend and family support to 52% for marital status and 59% for spouse support.

Bergeman et al. (2001) investigated the genetic and environmental determinants of social support over time in a longitudinal study of identical and fraternal twins from the Swedish Adoption/Twin Study of Aging. The study, which assessed friend and family support over three time points, found that social support is moderately stable over time and significantly heritable, with genetic correlations ranging from 65 to 97%

Not all aspects of social support appear to be equally influenced by genetics. Vinkhuyzen et al. (2010) analyzed the size of social support networks and satisfaction with social support in 560 Dutch twins and their siblings (59% females) from 256 families registered with the Netherlands Twin Register (NTR), with an average age of 47.11 years. While the size of social support networks showed modest heritability, satisfaction with social support did not. This variation highlights the complex picture of different dimensions of social support and genetic factors.

The Current Study

In this contribution, we seek to enhance the understanding of the heritability of social support by focusing on a large adult twin sample from the Netherlands. Given that prior research on the heritability of social support has predominantly been centered in the U.S., our study seeks to broaden this perspective by focusing on a large adult sample from the Netherlands. While not the first study of its kind in this region, our research employs a significantly larger sample size than previous Dutch studies (Vinkhuyzen et al., 2010), enhancing the statistical power of our findings. This is particularly relevant given the stark differences in welfare policies, such as those related to work-life balance and social security, which are more robust in European countries, especially the Scandinavian countries and the Netherlands but others as well, compared to the U.S. (Alesina & Glaeser, 2006). Exploring these genetic influences within such a distinct framework can provide deeper insights into the environmental interactions that shape social support.

Methods

Participants and Protocol

Participants were registered with the Netherlands Twin Register (NTR; Ligthart et al. 2019). Adolescent and young adult twins and their parents were initially recruited into the NTR through city Dutch council registrations, followed by recruitments via the NTR website and newsletters as well as publicity in the media. The present study is based on data from the eight wave of survey data collection that were collected between 2009 and 2011 (Geels et al., 2013). After obtaining approval from the Medical Ethics Committee of the VU University Medical Center Amsterdam, all NTR participants aged 18 years and older with a known valid address were invited to complete survey 8 (N=47,122). They first received a written invitation with a unique login name and password and a link to a webpage with a web-based version of the survey. If they did not access the web-based survey in the 6 weeks after the invitation, a hard-copy of the survey was sent. Between 3–9 months after the paper versions of the survey were sent out, non-responders received a reminder by post or email. Several groups of non-

responders were contacted by phone. This resulted in completion of the survey by 16,891 individuals. A final effort to increase response rates early in 2012 consisted of 3 extra mailings with the option to fill out a shorter version of the survey either on paper or online. This led to 3,436 additional responders (total N = 20,236). However, the shorter survey 8.1 did not contain the items on social support, hence for the current paper we analyze the data from the first, longer, version of survey 8 with phenotype information on social support, including 8,019 twins with no more than 2 missing items for the phenotype (see below). Twin zygosity was determined from DNA polymorphisms for 61% of all same-sex twin pairs and from harmonized longitudinal survey information for the others. Zygosity was missing for 124 twins, who had only completed surveys that did not contain questions on zygosity. The correspondence between zygosity based on survey items and on DNA is 97% (Ligthart et al., 2019; Willemsen, Posthuma, & Boomsma, 2005). The average age of the twins was 32.8 years (SD = 14.2).

The phenotype

The Duke – UNC Functional Social Support Questionnaire (FSSQ) asks people "To what extent do people around you give you help and support when needed?" (Broadhead et al., 1988). The FSSQ consists of 8 items (I have people who care what happens in my life; I get love and affection; I have the chance to talk to someone about problems at work or my home situation; I have the chance to talk to someone I trust about my personal problems; I have the chance to talk to someone about money matters; I'm invited to go out or do things with others; People give me valuable advice about important things in life; I get help when I'm sick in bed) that are scored on a 5 point scale, from "much less than I would like" to "as much as I would like". The reliability of the scale was good with a Cronbach's alpha of 0.89. The FSSQ allows for two specific dimensions of support: confident support and affective support. We performed a principal component analysis (PCA) on the 8 social support items to explore their dimensionality. The PCA identified several components with varying degrees of contribution to the total variance, evidenced by their eigenvalues. The first component had an eigenvalue of 4.656, indicating a strong underlying factor that accounted for

58.2% of the total variance. All other components had eigenvalues below 1 and did not contribute to more than 9% of the variance (see Table 4.1). Given this result, we chose to analyze the average score of all social support items, allowing for a maximum of 2 missing items. Notably, nearly 40% of participants had an average score of 5 (the highest possible score), leading to a highly skewed distribution of the data, as is displayed in Figure 4.1. We therefore dichotomized the social support score into 2 categories, with participants who had a lower average than 5 assigned a zero and all others a one.

Table 4.1. Results of Principal Component Analyses for the Eight Social Support Items.

Component	Eigenvalue	Percentage of Variance (%)
Component 1	4.66	58.20
Component 2	0.76	9.44
Component 3	0.62	7.81
Component 4	0.59	7.40
Component 5	0.43	5.35
Component 6	0.38	4.72
Component 7	0.36	4.55
Component 8	0.20	2.53

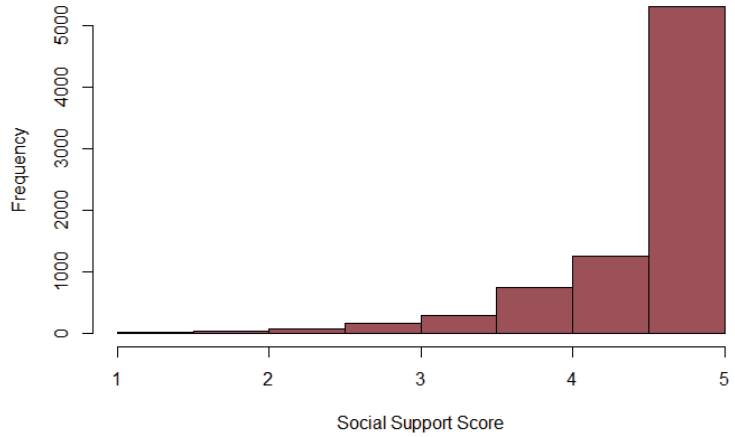

Figure 4.1. Distribution of mean social support score.

Statistical Analyses

Genetic analysis of the data employed a threshold model (Falconer & Mackay, 1996) in which a dichotomous variable is seen as the expression of an underlying continuous risk distribution called 'liability'. The threshold, which is estimated from the data, divides the sample into "affected" and "unaffected" subjects. Tetrachoric twin correlations were estimated to quantify the resemblance for liability in MZ and DZ twins, allowing for differences in correlation for men and women and for twins of opposite sex. The contributions of genetic and environmental factors to individual differences to liability can be inferred from the different level of genetic relatedness of MZ and DZ twins (see e.g. Posthuma et al., 2003). We decomposed the variance of the liability scale into variance due to additive genetic (A) influences, due to shared environment (C) and non-shared environment (E). The shared or common environment (C) is defined as those environmental influences that are similar for MZ and DZ twins, thus the shared environmental factors correlate 1.0 in both types of twins. Non-shared environmental influences are uncorrelated and also absorb uncorrelated error. Model fitting was performed with raw-data maximum likelihood in Mx (Neale et al., 2006), including all data from complete and incomplete twin pairs. Fixed effects were included for sex, age (standardized) and age (standardized) squared. A saturated model was specified first, and then constraints and an ACE and an AE model were tested by likelihood-ratio tests. When comparing nested models, a change in the -2 log-likelihood between models is distributed as a chi-square with degrees of freedom (df) equal to the differences in df between the models. A significant difference ($p<0.05$) when relaxing a constraint means that this constraint cannot be relaxed. We computed likelihood-based 95% confidence intervals (Neale & Miller, 1997).

Results

A fully saturated model, allowing for different estimates of thresholds in men and women, regressions of age (standardized) and age (standardized) squared on thresholds and 5 different twin correlations, gave -2LL = 10513.58 (df =7886). Table 4.2 presents the estimates for the 5 twins correlations and their 95% confidence intervals,

the average age and the age range in the sample and also shows the percentage of twins with the maximum score on social support. Constraining the two MZ (males and females) and three DZ correlations (same-sex males and females and opposite sex pairs) to be equal gave a -2LL = 10516.89 (df=7889). The chi-squared test statistic (3 df) thus is 3.31, indicating that MZ and all DZ correlations did not differ between men and women.

In this model the estimates for the regression of age (standardized) and age (standardized squared) were 0.002 and 0.011, respectively. The test of significance for the age regressions were non-significant (-2LL = 10518.517, df=7891). Thresholds in men and women were estimated at 0.32 and 0.24, respectively. The test if thresholds are the same in males and females also gave a non-significant difference in likelihood (-2LL = 10521.382 with df=7892).

For this last model table 2 also presents the correlations in all MZ and all DZ twins. The estimate of 0.38 for MZ pairs is almost twice the correlation in DZ pairs (0.17), suggesting a modest heritability and no or very little influence of shared environment.

Fitting an ACE model to the data confirmed this with heritability estimated at 41%. The ACE model (including 1 constraint on total variance) gave -2LL = 10521.382 (df = 7892). Omitting the influence of common environment was clearly permitted with a minimal difference in goodness of fit (-2LL = 10521.514, df = 7893). Heritability in the AE model was estimated at 37% (see also Table 4.3).

Table 4.2. Estimates for Tetrachoric Twin Correlations and 95% Confidence Interval.

Type	r	CI	N complete pairs	Average age (range) ; SD	N twins	Maximum score social support (%)
MZF	0.414	0.329 - 0.493	1,096	34.8 (17-90) ; 14.9	2,866	41.28
DZF	0.206	0.067 - 0.340	484	32.3 (18-86) ; 13.4	1,496	40.84
MZM	0.266	0.104 - 0.417	369	34.2 (17-82) ; 15.0	1,071	37.91
DZM	0.183	-0.052 - 0.402	184	32.4 (18-81) ; 14.4	656	38.87
DOS	0.130	-0.018 - 0.273	462	29.8 (18-78); 12.7	1,806	38.65
All MZ	0.379	0.304 - 0.451	1465	34.6 (17-90) ; 14.9	3,937	39.59
All DZ	0.172	0.079 - 0.262	1130	31.0 (18-86) ; 13.3	3,958	39.25

Note: MZF = Monozygotic Female pairs, DZF = Dizygotic Female pairs, MZM = Monozygotic Male pairs, DZM = Dizygotic Male pairs, DOS = Dizygotic Opposite Sex pairs.

Table 4.3. Estimates for variance components and 95% confidence interval from ACE and AE model.

Component	Full model Estimate (CI)	Reduced Model Estimate (CI)
Additive genetic variance (A)	0.415 (0.403 - 0.649)	0.3733 (0.303 -0.440)
Common environmental variance (C)	-0.036 -0.235 - -0.036	-
Unique Environmental variance (E)	0.621 (0.621 - 0.656)	0.6257 (0.558-0.695)

Discussion

Our study highlights the contribution of genetic factors in shaping individual differences in social support. The contribution is modest, with heritability estimated at 37%, but too large to label social support as an environmental trait. Labeling traits as 'environmental' ignores that they are often not randomly distributed within a population but reflect heritable individual differences (Plomin & Bergeman, 1991; Vinkhuyzen et al., 2010). Social support is often labeled as an environmental measure and viewing it as such may have, perhaps unintended, consequences. People in aging populations, for example, face changes and challenges with loss of social contracts because of retirement, loss of loved ones and health issues leading to decreased mobility and independence. Social support, which can include emotional, instrumental, and informational assistance from others, may mitigate these challenges and strong social support systems can help to buffer the negative effects of aging-related changes and contribute to better physical and mental health outcomes. Governments recognize the importance of investing in social support, and advice to build social networks early in life, but may not always appreciate that differences between people in their social support networks may be influenced by genetic liabilities.

Our findings support the genetic basis of social support and align with other studies across different populations, including the US, Sweden and the UK, which also demonstrated significant genetic contributions, with figures ranging widely but consistently indicating a notable genetic component (Bergeman et al., 2001; Kendler, 1997; Wang et al., 2017). These studies as well as our own findings reinforce the concept that social support encompasses both genetic and environmental factors. As these findings are based on data from twins, one could wonder if twins experience more social support because of a close bond between some of them, or that MZ twins experience more social support (from each other) than DZ twins. However, previous research found no evidence to support these claims. For example, Willemsen et al. (2021) carried out a within-family analysis to test if there are mean differences between

twins and (non-twin) singletons, i.e. they compared twins to their siblings across a large number of traits, including the two subscales of the Duke – UNC Functional Social Support Questionnaire, and found no differences between twins and siblings. We also tested whether the prevalence of reported social support differed between MZ and DZ twins using a generalized estimating equation (GEE) to account for clustering. The analysis revealed no difference in the distribution of social support between MZ and DZ twins ($\beta = 0.035$, SE = 0.048, $p = 0.461$), indicating that both MZ and DZ twins report social support at comparable rates.

It should be noted that the significant genetic contribution does not, however, diminish the role of non-genetic factors. Unique environmental factors were found to account for a substantial portion of the variance (63%), underscoring the dual impact of genetic predispositions and unique environmental experiences on social support networks.

There is a multitude of different instruments to assess social support, and differences in heritability across studies may therefore not simply be interpreted as evidence reflecting differences in welfare state. These variations may point to the sensitivity of heritability estimates to the specific methods and instruments used in their assessment. Future research should critically evaluate the design and application of these instruments to ensure that they accurately capture the nuances of social support as it is experienced in different social and cultural contexts. Additionally, the variability in heritability estimates across different types of social support may suggest that genetic influences are modulated by varying environmental contexts and social structures. This indicates a complex interaction between genetics and environment, which can differ significantly depending on the nature of the social systems and types of support involved. Future research should focus on disentangling the specific environmental conditions that amplify or mitigate genetic influences on social support. Studies could explore how cultural differences impact the expression of genetic predispositions toward social support or investigate the role of specific life events, such as victimization, migration or significant personal losses, in shaping these dynamics. Furthermore, longitudinal studies that track changes in social support

across different life stages could provide deeper insights into how the interplay between genes and environment evolves over time.

In conclusion, our study underscores the importance of considering both genetic and environmental influences when studying social support systems. This result is a valuable addition to existing discussions of how factors, such as social support, shape individual differences in behavior and have crucial implications for understanding the complex nature between genetic and environmental influences on complex traits.

Chapter 5.

Social Support and Health Outcomes in Crime Victims

Abstract

Crime victimization is associated with poor physical and mental health. We sought to understand the role of social support as a protective factor among victims. Self-report data from the Netherlands Twin Register (NTR) for 15,884 individuals aged 18 and older, including twins and their family members, were analyzed. Multivariate analyses revealed that victimization, particularly after sexual assault, was significantly associated with poorer general health and increased depression. Looking at social support, a lower level of support was associated both with poorer general health and increased depression. In moderation analyses, social support emerged as protective after victimization, especially for those who experienced sexual and violent crimes and to a lesser extent for property crimes. Analyses in monozygotic (MZ) and dizygotic (DZ) twin pairs discordant for victimization controlled for shared environmental and partial genetic confounding. These analyses indicated that violent and property crime victimization were not associated with negative health consequences, either in terms of general health or depression. However, sexual crime victimization was associated with negative general health outcomes, supporting a causal hypothesis. Social support had a main effect on depression in all discordant twin analyses. Moderation analyses showed that the protective effects of social support after victimization were complex. While higher social support significantly buffered the general health consequences of violent victimization in combined MZ and DZ discordant twin pairs, this interaction effect was not significant in MZ discordant twin pairs. All other interaction effects observed in the multivariate analyses also failed to emerge in the discordant twin analyses. This suggests that while social support may appear to buffer the negative health impacts of crime victimization, this effect is partly due to genetic and shared environmental factors. These findings underscore the importance of accounting for genetic and shared environmental confounding in future research to fully understand the relationships among victimization, social support, and health outcomes.

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Social Support and Health Outcomes in Crime Victims

Crime victimization may have far-reaching implications for individual well-being. Victims of crime often endure not only immediate physical harm but also experience long-term psychological and emotional consequences (Ann Priester et al., 2016; Britt, 2001; Tan & Haining, 2016). Understanding the health impacts of crime victimization is crucial, as these effects extend beyond the initial incident, potentially leading to chronic health conditions and diminished quality of life. Understanding the causal paths of these effects is necessary to develop interventions to mitigate these adverse outcomes and improve the well-being of victims.

The association between victimization and health is likely complex and influenced by multiple factors, via multiple pathways. Beyond the possible direct physical injuries from crime, the psychological trauma from crime can trigger stress responses that exacerbate mental health issues such as anxiety, depression, and post-traumatic stress disorder (PTSD) (Bouffard & Koeppel, 2014; Tan & Haining, 2016). Physiologically, chronic stress associated with victimization may contribute to various physical health problems, including cardiovascular disease, weakened immune function, and chronic pain (e.g. Britt, 2001). The seriousness of these health outcomes stresses the need to explore factors that might influence the adverse effects of victimization. One factor that could have a mitigating effect on the adverse consequences of crime victimization is social support.

Social support has been linked to better mental and physical health, as it provides a sense of belonging and security (Harandi, Taghinasab, & Nayeri, 2017). For example, individuals with strong social networks often experience lower levels of anxiety, depression, and stress-related health problems (Kaniasty & Norris, 2008). However, it can also work the other way around: through the process of social selection, individuals with more severe mental health problems may experience a decline in social support over time (Kaniasty & Norris, 2008) and individuals with physical health problems encounter barriers to participate in society, which can lead to social isolation (Tough, Siegrist, & Fekete, 2017). Given the established link between social support and health, a logical

step is to investigate if social support might moderate the relationship between victimization and health outcomes. The buffering hypothesis suggests that social support can mitigate the impact of stressful events, such as victimization, on health by providing resources that help individuals cope more effectively (Cohen & McKay, 2020). This suggests that individuals with strong social support systems may experience fewer negative health consequences following victimization. Much of the existing research has focused on the potential moderating effect of social support on the relationship between victimization and mental health outcomes. For example, Scarpa, Haden and Hurley (2006) examined the impact of social support and coping styles on the severity of posttraumatic stress disorder (PTSD) following exposure to crime victimization among 372 adolescents. Their findings indicated that the expected protective benefits of high social support decreased as victimization severity increased. Holt and Espelage (2005) examined how social support moderated the relationship between dating violence victimization and mental health outcomes in adolescents (N = 681). Their research highlighted that social support significantly reduced the effects of both physical and emotional abuse on anxiety and depression, particularly among African American males. Similarly, Denkers (1999) looked at needed and received support among victims of crime (N = 5,218) and found that receiving less support than needed was associated with low well-being, both before and after the crime. This was especially the case for partner support. This pattern of findings, emphasizing the importance of social support in alleviating the negative impacts of victimization, extends to younger populations as well. For instance, Chan et al. (2017) explored how family structure and social support impact the health consequences of violent victimization in a large sample of 4,139 school-aged Chinese children. Both family structure and social support reduced the negative health consequences of child victimization. Crush et al. (2018) examined the protective role of social support in mitigating psychotic experiences at age 18 in a cohort of 2,232 UK-born twins, including a high-risk group exposed to multiple victimization at the ages of 12 - 18. Increased social support was protective against adolescent psychotic experiences amongst those exposed to poly-victimization, even after controlling for variables like gender, socioeconomic status, family psychiatric history, and early mental health issues.

However, not all research has found social support to be protective against the negative impacts of victimization. Burke, Sticca and Perren (2017) examined peer victimization among 960 Swiss children and found it was positively associated with depressive symptoms, but while parental and friendship support had a positive impact on adolescents' well-being, it did not buffer the effects of peer victimization on depressive symptoms.

Overall, most previous studies have demonstrated that social support is associated with a reduced likelihood of a wide range of adverse (health) outcomes in individuals who have experienced victimization. Most of this previous research have thus generally supported the idea that social support serves as a protective buffer against the harmful impacts of victimization. However, understanding the underlying mechanisms of this relationship is complex. While there might be a direct causal relationship, where social support around the time of victimization directly mitigates the effects of victimization on health, it is also possible that concurrent social support is connected to other, shared, environmental factors. For instance, individuals nurtured in supportive family and community settings are likely to develop stronger social networks and healthier coping mechanisms, which may lessen the impact of victimization on their health and mental well-being. Conversely, those from less supportive environments may face greater challenges in coping with similar adversities (Blain, Thompson, & Whiffen, 1993; Crush et al., 2018). This suggests that the observed protective effects of social support might partly be due to the shared environmental background, rather than concurrent social support alone. Genetic factors might also play a role in susceptibility to health problems and mental health issues following victimization but can also influence the degree of social support that is perceived or experienced. Heritability studies have found the heritability of health problems and mental health outcomes to be moderate to high. For example, the meta-analyses of Polderman et al. (2015) estimated the heritability of mental health problems to be 46.3%. Even though victimization might seem a chance occurrence, it does not happen at random and heritable traits have been identified that are associated with an increased risk of victimization (Beaver et al., 2009; Veldkamp et al., 2019). This does not imply that genes directly cause people to become victims, but

rather that there are genetic effects in personal characteristics, such as behaviors or personality traits, that increase an individual's risk for being victimized. While self-reported social support may often be considered an environmental factor, it is itself also influenced by genetic factors with its heritability estimated at 37% (Gonggrijp, van de Weijer, Bijleveld, van Dongen, & Boomsma, 2024). The relationship between victimization, social support and health outcomes might therefore be influenced by (shared) environmental and genetic factors that affect both social support and vulnerability to health problems after victimization.

The Current Study

This study adds to the existing literature by examining the potential moderating effects of social support on the relationship between victimization and health problems while controlling for genetic and shared environmental confounders. The discordant twin design is particularly valuable in this context (Gonggrijp et al., 2023; van Dijk, Norris, & Hart, 2022). By studying twins who are discordant for victimization— one twin has been victimized and the other has not—we control for genetic and shared environmental factors. By examining data from dizygotic (DZ) twins, who share approximately 50% of their genes, and monozygotic (MZ) twins, who are genetically identical, and noting that both types of twins have shared environment, this design provides a robust framework to explore how social support can mitigate the adverse effects of victimization. If an association that is observed in the general sample, is diminished in discordant twin pairs, it suggests that genetic and shared environmental factors contribute to the association. Conversely, if the association remains robust within discordant twin pairs, it indicates that concurrent social support has an effect that survives after correcting for genetic and shared environmental background. This approach allows for a more nuanced understanding of how social support moderates the health and well-being of individuals who have experienced victimization, while correcting for possible genetic and environmental confounding.

To investigate these dynamics, this research will explore both mental and general health outcomes following victimization in a large adult Dutch sample. We first examine the

associations between victimization (i.e., victimization of sexual, violent and property crimes), self-rated health (SRH), and depression in the general sample. This model allows us to determine if an association exists between victimization and these health outcomes. Next, we investigate the role of social support by incorporating interaction terms between social support and each type of victimization. This approach will help us understand whether social support moderates the impact of different types of victimization on health outcomes. Then, by employing a discordant twin design both in all same sex discordant twin pairs and MZ twin pairs separately, we aim to effectively control for potential confounding factors, such as shared environmental influences and genetic factors. For the discordant twin analyses, we again do this in two steps: first, we examine the main effects of victimization on health outcomes, and then we include interaction terms between social support and victimization to assess social support's moderating role.

Methods

Cohort Description

The data analyzed in this study were collected from twins, their parents, siblings, spouses, and offspring who take part in studies of the Netherlands Twin Register (NTR). The NTR, established over 30 years ago by the Department of Biological Psychology at Vrije Universiteit Amsterdam, gathers data from both children and adults. The Adult NTR (ANTR) collects longitudinal survey data every two to three years. These surveys cover aspects such as lifestyle, personality, psychopathology, and well-being within twins and their families. Detailed information on the data collection procedures in the NTR can be found elsewhere (e.g. Ligthart et al. 2019; Middeldorp et al. 2008).

The present study is based on data from the 8th wave of survey collection, that was carried out between 2009 and 2011. The survey had two versions, a full version and a shortened version. We include only data from the full version (N = 16,891), as the short version did not include information about victimization and social support (Geels et al., 2013; Gonggrijp et al. 2024). We included participants aged 18 years and older in the study (excluded participants younger than 18: N = 21). If participants had not answered

questions on victimization (N = 547), general health and depression (N = 23), or social support (N = 416) they were also excluded from the analyses. This resulted in a total sample size of 15,884 individuals which included 8,005 multiples (twins and triplets), 1,775 siblings, 5,036 parents, and 1,068 other participants (spouses, offspring and other family members of twins). For the discordant twin analyses, all twin pairs with missing zygosity were further removed from the analyses (N = 12) and only the same-sex twins discordant for at least one type of victimization were selected. This resulted in a total sample of 599 MZ and 293 DZ discordant twin pairs in these analyses.

Exposure

Victimization

The 8th survey included a Dutch life event scale (the Schokverwerkings Inventarisatie Lijst; Van der Velden et al., 1992), asking: 'What events have happened to you in your life?'. The life events included property crime (theft, burglary, vandalism), violent crime (robbery, physical assault), and sexual offense (rape, assault). Response categories were "never experienced", "less than a year ago", "1–5 years ago" and "more than 5 years ago". For both the population and discordant twin analyses, the victimization experience was dichotomized to ensure sufficient sample size by combining all experiences of victimization into a single category, regardless of the timing, and comparing them against never experiencing victimization.

Outcomes

Self-Rated Health (SRH)

SRH was measured with the single item 'In general, how would you rate your health?'. There were five answer options which are scored on a five-point scale with 1 = "bad", 2 = "mediocre", 3 = "reasonable", 4 = "good", and 5 = "excellent". This single item assessment of SRH is recommended by the World Health Organization (WHO) and validated across many studies and contexts (Ahmad et al., 2014; Bardage et al., 2005; Chandola & Jenkinson, 2000). Participants generally reported good health, with an average score of 4.54 (SD = 0.65) out of 5, indicating a positive self-assessment of health status among the majority of the sample.

Depression

Depression was measured by the Adult Self Report (ASR) (Achenbach, Dumenci, & Rescorla, 2003). In the ASR, participants report their behavior, thoughts, and feelings of the previous 6 months by rating how applicable the items are. Each item is rated from 0 = not true, 1 = somewhat true, to 2 = very true. Two example items are "*I am unhappy, sad, or depressed*" and "*I do not have much energy*". The empirically validated ASR depression scales included 18 items that were summed to create a total depression score (range 0 – 36). To increase the number of data points, we imputed missing data using mean imputation. The total scale score was only computed, and missing data imputed, when two or less than two items of the complete scale were missing. Depression level was generally low within the sample (mean = 4.90, SD = 5.22).

Support

Social Support

Social support was assessed by the Duke-UNC Functional Social Support Questionnaire (FSSQ; Broadhead et al. 1988) which consists of 8 items to rate the amount of support received on a 5-point Likert scale (1=much less than I would like and 5=as much as I would like). An example item states "I receive love and affection from others". A higher average score indicates greater perceived social support. The FSSQ allows for calculation of a total score, and two specific dimensions of support: confident support and affective support. A principal component analysis of the items indicated one functional social support dimension in the data (Gonggrijp et al., 2024). Reliability of this scale was excellent based on the Cronbach's alpha (0.9). Notably, 38,76% of participants had an average score of 5 (the maximum) across all items, highlighting a high level of received support within the sample, but also resulting in a highly skewed distribution of the data. Following Gonggrijp et al. (2024), the total social support score was dichotomized: high social support with an average of 5 across all items, and lower social support with an average below 5 across all items. Prior to dichotomization, participants with a maximum of two missing items were included in the analysis by imputing the missing values with the mean score of their available responses.

Statistical Analyses

A Generalized Estimating Equation (GEE) linear regression model was applied with victimization as the exposure and SRH and depression as the outcome variables in the entire sample (population design) in R. This was done to determine if associations were present between victimization and SRH and depression. To account for possible age or sex effects, sex and age (centered at the mean age) at the time of the survey were included in the model. To account for familial clustering the GEE model was specified to adjust for the correlation between observations within the same family. The general structure of the regression model [1] is as follows:

$$Outcome = \beta_0 + \beta_1\, violent\ crime + \beta_2\, sexual\ crime + \beta_3\, property\ crime + \beta_4\, sex + \beta_5\, age(centered) + \epsilon$$

To understand the role of social support (SS), interaction terms between social support and each type of victimization were added to the GEE models. The interaction model[1] is specified as:

$$Outcome = \beta_0 + \beta_1\, violent\ crime + \beta_2\, (violent\ crime\ x\ SS) + \beta_3\, sexual\ crime + \beta_4\, (sexual\ crime\ x\ SS) + \beta_5\, property\ crime + \beta_6\, (property\ crime\ x\ SS) + \beta_7\, SS + \beta_8\, sex + \beta_9\, age(centered) + \epsilon$$

A co-twin control analysis in all same-sex twin pairs was implemented on a subset of monozygotic (MZ) and dizygotic twin (DZ) pairs identified as discordant for the experience of at least one type of victimization. This means that within each pair, one twin reported experiencing a certain type of victimization (e.g., property crime, violent crime, or sexual crime) while the co-twin did not. By comparing outcomes between these discordant twins, we can effectively control for genetic factors (approximately shared by 50% in the DZ twins and 100% in the MZ twins) and family-level environmental

[1] For clarity, we have omitted the indices for individual (i) and family (j) in the regression equation, as this analysis does not make within-family comparisons. However, it should be noted that there are familial clusters in the data. The GEE model adjusts for the correlation between observations within the same family to account for this clustering. All β's are population parameters. All variables, both predictors and outcomes, and the error term, are measured at the individual level within families.

influences, since these are constant within each twin pair. This design allows us to more accurately attribute any differences in outcomes to the experience of victimization itself, rather than to other confounding factors. A fixed effects regression analysis was then conducted to evaluate both outcomes (i.e., self-control and depression), leveraging the within-pair comparison to draw more precise conclusions about the impact of victimization. Sex and age were not included in the model as these variables are inherently controlled for within (same-sex) twin pairs. Social support was examined first as a main effect and, in the second model, as an interaction with victimization to assess its moderating role.

The general structure of the regression model is as follows:

$$\left(Outcome_{ij} - \overline{Outcome_i}\right) =$$
$$\beta_1\left(violent\ crime_{ij} - \overline{violent\ crime_i}\right) + \beta_2\left(sexual\ crime_{ij} - \overline{sexual\ crime_i}\right) +$$
$$\beta_3\ \left(property\ crime_{ij} - \overline{property\ crime_i}\right)\ + \beta_4\ \left(SS_{ij} - \overline{SS_i}\right) + \left(\epsilon_{ij} - \bar{\epsilon}_i\right)$$

where i indexes the family (twin pair) and j indexes the individual twin within each family. The overbar notation (e.g., $\overline{Outcome_i}$) denotes the mean value of the variable within family i. Thus, for example, $(Outcome_{ij} - \overline{Outcome_i})$ is the difference between the outcome for twin *j* in pair i minus the mean outcome of pair i. The interaction model is specified as follows:

$$\left(Outcome_{ij} - \overline{Outcome_i}\right) =$$
$$\beta_1\left(violent\ crime_{ij} - \overline{violent\ crime_i}\right)$$
$$+ \beta_2\left(violent\ crime_{ij}\ x\ SS_{ij} - \overline{violent\ crime_i}\ x\ \overline{SS_i}\right) +$$
$$\beta_3\left(sexual\ crime_{ij} - \overline{sexual\ crime_i}\right)$$
$$+\ \beta_4\left(sexual\ crime_{ij}\ x\ SS_{ij} - \overline{sexual\ crime_i}\ x\ \overline{SS_i}\right) +$$
$$\beta_5\ \left(property\ crime_{ij} - \overline{property\ crime_i}\right) + \beta_6\ \left(property\ crime_{ij}\ x\ SS_{ij} -\right.$$
$$\left.\overline{property\ crime_i}\ x\ \overline{SS_i}\right)\ + \beta_7\ \left(SS_{ij} - \overline{SS_i}\right) + \left(\epsilon_{ij} - \bar{\epsilon}_i\right)$$

To account for multiple testing, we calculated q-values for all p-values using the false discovery rate (FDR) method, implemented with the R package q-value. The FDR method is a statistical procedure used to control the expected proportion of false positives

among the set of significant results (Benjamini & Hochberg, 1995). The q-value is a measure derived from the FDR method that indicates the minimum FDR at which a particular test result is considered significant. In other words, the q-value represents the proportion of false positives we are willing to accept among all significant results. For this study, we set a significance threshold for q-values at 0.05, meaning we allow up to 5% of our significant findings to be false discoveries.

Results

Descriptives Statistics

Participants had ages ranging from 18 – 89 years (Mean = 40.67, SD = 15.73). The majority of the sample identified as female (63.84%). Table 5.1 gives the victimization frequency of sexual crimes, violent crimes, and property crimes, separately for the entire sample and all of the twins (i.e., same-sex discordant, opposite-sex, and concordant twins). Property crime had the highest prevalence and was slightly higher in the entire sample (30.65%) compared to the twins (27.23%). The lowest prevalence was for experiencing violent crimes, in the general sample (6.07%) as well as for the twins (6.48%).

Figure 5.1 displays the average score on SRH and depression per type of victimization for the entire sample and all twins separately. Social support had been divided into two groups; high and low social support. A higher depression score was seen for victims compared to non-victims, which was most pronounced in the group of low social support. Furthermore, a decrease in SRH was displayed for victims compared to victims,

Table 5.1. Victimization frequencies of sexual, violent, and property crime for the entire sample, and separately for the twins.

	Entire Sample					
	Sexual Crime		**Violent Crime**		**Property crime**	
	N	**%**	**N**	**%**	**N**	**%**
Not experienced	14652	93.71%	14709	93.93%	10921	69.35%
Experienced	983	6.29%	951	6.07%	4827	30.65%
	All Twins					
Not experienced	7158	93.32%	7183	93.52%	5609	72.77%
Experienced	512	6.68%	498	6.48%	2099	27.23%

again most strongly among those with low social support. The only exception was for property crime victimization, where there were minimal to no differences. These patterns were similar for both the entire sample as for the twins.

Self-Reported Health

Table 5.2 reports the results from the GEE analyses on SRH. The table includes results from two models: the model without interaction effects, which included all variables, and the interaction model, which also included interaction terms between victimization types and social support. In the model without interaction effects sex (B = -0.100, q= 5.10E-18) and age (B = 0.008, q = 1.13E-124) were significantly negatively associated with SRH, meaning that SRH is lower among older participants and women compared to younger participants and men. More importantly, both violent and sexual crimes also showed a negative association with SRH, indicating that experiencing a violent (B = -0.107, q = 1.35E-05) or a sexual crime (B= - 0.246, q = 1.76E-25) is related to lower SRH compared to non-victims. However, experiencing property crime was not associated with SRH (B = 0.018, p = 0.206). Additionally, social support showed a significant positive association with SRH, showing that higher social support is linked with better SRH outcomes (B = 0.190, q = 6.61E-64).

Table 5.2. Generalized Estimating Equations (GEE) Analysis of Self-Reported Health (SRH) Considering Main Effects and Interaction with Social Support in the total sample (N = 15,396).

	Model 1: without Interaction			**Model 2: with Interaction**		
Variable	**B**	**SE**	**q**	**B**	**SE**	**q**
Intercept	4.101	0.011	0.00E+00*	4.114	0.011	2.75E-06*
Violent Crime	-0.107	0.023	1.35E-05*	-0.140	0.029	8.65E-26*
Sexual Crime	-0.246	0.023	1.76E-25*	-0.292	0.027	0.714
Property Crime	0.018	0.012	0.206	-0.007	0.015	3.96E-126*
Sex (1 = female)	-0.100	0.011	5.10E-18*	-0.100	0.011	7.22E-30*
Age (centered)	-0.008	3.51E-04	1.13E-124*	-0.008	3.51E-04	7.60E-18*
Social Support (SS)	0.190	0.011	6.61E-64*	0.156	0.014	0.051
Violent Crime * SS				0.109	0.049	0.002*
Sexual Crime * SS				0.163	0.050	0.018*
Property Crime * SS				0.064	0.024	2.75E-06*

Note: B = unstandardized coefficient, SE = standard error of the coefficient, q = FDR q-value; adjusted p-value after accounting for multiple comparisons. * < 0.05

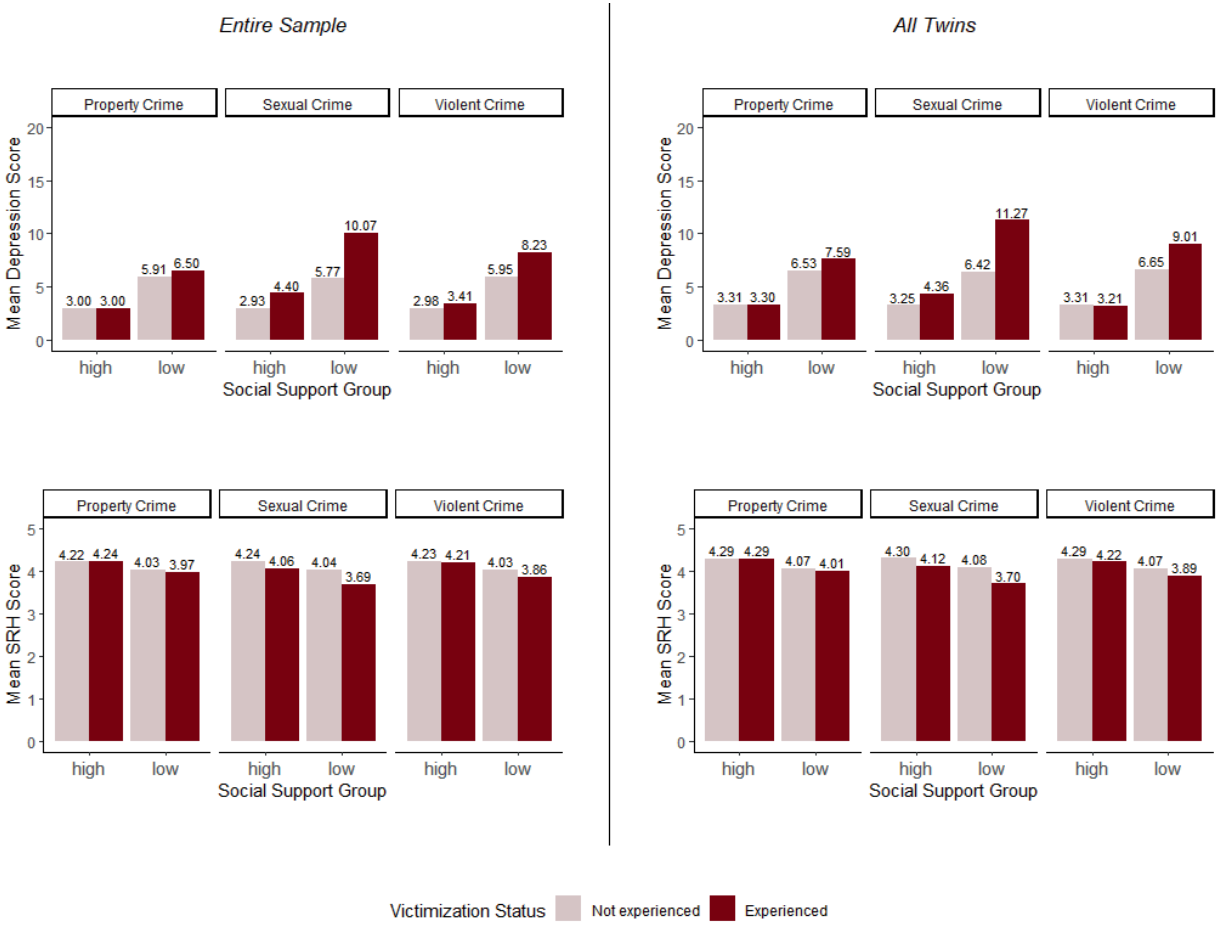

Figure 5.1. Average depression and self-reported health scores, per type of victimization, for those who experienced high or low level of social support, among the entire sample and separately for all twins.

To assess the potential moderating effects of social support on the association between victimization experiences and SRH, interaction terms were added to the GEE analyses. In the interaction model, the main effects of violent crime on SRH were significant and negative, consistent with the model without interaction effects. These main effects apply to the group with low social support, indicating that experiencing a violent crime while having low social support leads to a decrease in SRH (B = -0.140, q = 8.65E-26), compared to non-victims with low support. Similarity, a negative association was found for experiencing property crimes on SRH (B= - 007, p = 3.96E-126). The interaction terms revealed that social support moderated the relationship between all types of victimization and SRH, indicating that victims with higher social support experienced less negative health effects compared to those with lower social support. These findings are illustrated in Figure 5.2A, which depicts SRH scores for both victims and non-victims, categorized by their levels of social support (high and low). The lines represent the estimated SRH scores based on the GEE model. The difference in SRH between the victims and non-victims is more pronounced when both have low social support. Conversely, this disparity diminishes when both groups receive high social support. This effect is particularly pronounced among victims of sexual and violent crimes. Those with low social support have substantially lower SRH scores compared to non-victims with similarly low support. However, when both groups have high social support, the difference in SRH scores narrows considerably. In the case of property crimes, the SRH score difference between victims and non-victims remains minimal, irrespective of social support levels. This highlights the moderating effect of social support on the relationship between victimization and SRH, indicating that higher social support can mitigate the negative impact of victimization on health outcomes.

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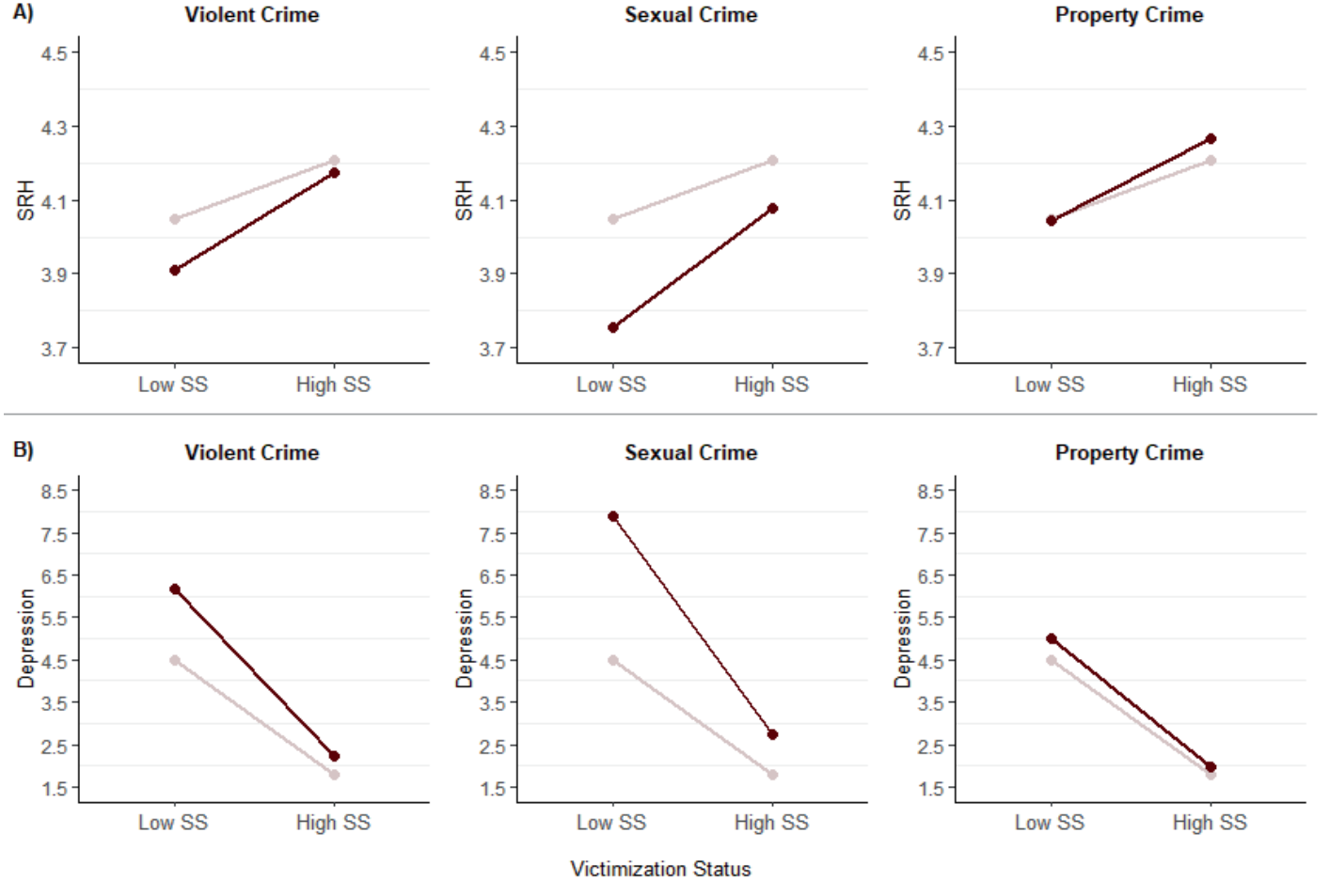

Figure 5.2. Interaction Victimization and Social Support Level on Self-Reported Health (**A**) and Depression (**B**). The lines represent the predicted values calculated from the unstandardized coefficients (B) obtained from the GEE model

Depression

Parallel to our investigation of SRH, GEE analyses were employed to evaluate the main effects on depression. Table 5.3 presents the outcomes of these GEE analyses, detailing the main effects of victimization, social support, sex and age on depression without considering interaction terms. All types of victimization showed a significant positive association with depression, indicating that victimization is linked to higher depression scores. The strongest association was again found for sexual crimes (B = 2.709, q = 3.29E-53), followed by violent crime (B = 1.302, q = 7.59E-13) and property crime (B = 0.402, q = 3.30E-05). Additionally, social support demonstrated a significant negative association with depression (B = -2.989, q = 1.14E-270), indicating that higher social support is linked to lower depression scores. Age also showed a significant negative association with depression (B = -0.046, q = 1.24E-61), suggesting that older individuals report lower levels of depression. Lastly, sex was significant positively associated with depression (B = 1.647, q = 6.96E-79), indicating that women had higher depression scores compared to men.

To study the moderating effects of social support on the relationship between victimization experiences and depression, interaction terms were included in the GEE analyses. The interaction model results are also presented in Table 5.3. The main effects in the interaction model remained similar to those in the model without interaction, with all types of victimization and social support continuing to show significant positive associations with depression. The interaction between violent crime and social support was significant (B = -1.277, q = 0.001), indicating that the association between violent crime and increased depression is stronger for individuals with low social support.

Similarly, the interaction between sexual crime and social support was significant (B = -2.494, q = 1.01E-10), suggesting that higher social support mitigates the impact of sexual crime on depression. However, the interaction between property crime and social support was not significant (B = -0.336, q = 0.115), indicating that social support does not significantly alter the effect of property crime on depression. These findings are illustrated in Figure 5.2B, which shows the depression scores for both victims and non-

Table 5.3. Generalized Estimating Equations (GEE) Analysis of Depression Considering Main Effects and Interaction with Social Support in the total sample (N =13,402).

	Model 1: without Interaction			Model 2: with Interaction		
Variable	**B**	**SE**	**q**	**B**	**SE**	**q**
Intercept	4.618	0.085	0.00E+00*	4.505	0.088	0.00E+00*
Violent Crime	1.302	0.177	7.59E-13*	1.707	0.217	1.29E-14*
Sexual Crime	2.709	0.175	3.29E-53*	3.424	0.206	3.92E-61*
Property Crime	0.402	0.092	3.30E-05*	0.531	0.116	1.35E-05*
Sex (1=female)	1.647	0.087	6.96E-79*	1.637	0.087	2.45E-78*
Age	-0.046	0.003	1.24E-61*	-0.045	0.003	7.31E-61*
Social Support (SS)	-2.989	0.085	1.14E-270*	-2.684	0.103	7.48E-149*
Violent Crime * SS				-1.277	0.372	0.001*
Sexual Crime * SS				-2.494	0.376	1.01E-10*
Property Crime * SS				-0.336	0.185	0.115

Note: B = unstandardized coefficient, SE = standard error of the coefficient, q = adjusted p-value the significance level of the coefficient after accounting for multiple comparisons. * q < 0.05

victims, categorized by their levels of social support. The figure clearly shows that the difference in depression between victims and non-victims of violent and sexual crimes is more pronounced when both have low social support. When both the victims and non-victims have high social support, the difference in depression scores is reduced. For victims of property crimes the depression scores of victims and non-victims show little difference, no matter the level of social support.

Similarly, the interaction between sexual crime and social support was significant (B = -2.494, q = 1.01E-10), suggesting that higher social support mitigates the impact of sexual crime on depression. However, the interaction between property crime and social support was not significant (B = -0.336, q = 0.115), indicating that social support does not significantly alter the effect of property crime on depression. These findings are illustrated in Figure 5.2B, which shows the depression scores for both victims and non-victims, categorized by their levels of social support. The figure clearly shows that the difference in depression between victims and non-victims of violent and sexual crimes is more pronounced when both have low social support. When both the victims and non-victims have high social support, the difference in depression scores is reduced. For

victims of property crimes the depression scores of victims and non-victims show little difference, no matter the level of social support.

Discordant Twin Design

The fixed effects regression analyses among twins discordant for victimization provided insights into the causal relationship between victimization experiences, social support, and SRH. Table 5.4 summarizes the results for SRH and depression among both MZ and SS DZ discordant twin pairs, as well as for the MZ discordant twin pairs separately.

Self-Reported Health

In the model that did not include the interaction terms with social support among MZ and DZ discordant twin pairs, experiencing sexual crime was significantly associated with lower SRH (B = -0.235, q = 0.002). The effect size was very similar to the analysis in the entire sample (B = -0.246, q = 1.76E-25). However, victimization of neither violent crime (B = -0.059, q = 0.064) nor property crime (B = -0.025, q = 0.986) were significantly associated with SRH. For the MZ discordant twin pairs, the negative association between sexual crime and SRH was not significant (B = -0.162, q = 0.164). Violent crime (B = -0.077, q = 0.324) and property crime (B = 0.017, q = 0.425) were also not significantly associated with SRH.

As in the analyses of the entire sample, interaction terms were included in the second model of the discordant twin analyses. In the MZ and DZ pairs analysis, experiencing sexual crime was again significantly associated with lower SRH (B = -0.235, q = 0.014), with the effect size again similar to the analysis in the entire sample (B = -0.292, q = 8.65E-26). The analysis among MZ discordant twin pairs also showed a significant main effect of experiencing sexual crimes (B = -0.186, q = 0.035), with a slightly decreased coefficient after the additional correction. Furthermore, the interaction between experiencing a violent crime and social support was significant in the DZ and MZ discordant sample (B = 0.127, q = 0.029), with the effect size similar to the analysis among the entire sample (B = 0.109, q = 0.002). This suggests that social support moderates the impact of violent crime on SRH, even after correcting for shared environmental factors and partly for

genetic factors. However, the MZ discordant twin pair analyses did not reveal a significant effect for the interaction between violent crimes and social support.

Depression

Parallel to the analyses on SRH, we evaluated the main effects of victimization experiences and social support on depression in the discordant twin sample. Table 5.4 details these outcomes for both MZ and DZ twin pairs, as well as for MZ twin pairs separately. In the combined sample of MZ and DZ discordant twin pairs, social support was significantly negatively associated with depression with very similar effect sizes when compared to the population analysis (B = -2.593, q = 7.06E-12), indicating that higher levels of social support were linked to lower depression scores. However, none of the types of victimization—sexual crime (B = 0.736, q = 0.102), violent crime (B = 0.363, q = 0.364), or property crime (B = 0.311, q = 0.461)—were significantly associated with depression. For the MZ discordant twin pairs, social support continued to show a significant negative association with depression, although the effect size was slightly reduced (B = -2.071, q = 3.80E-08). This shows that while social support consistently relates to lower depression scores, the effect is partially attributable to genetic factors. Victimization experiences, including sexual crime (B = 0.628, q = 0.518), violent crime (B = 0.558, q = 0.170), and property crime (B = -0.067, q = 0.950), were not significantly associated with depression in the analysis among MZ pairs.

Table 5.4. Results of the discordant twin analyses of victimization on self-reported health and depression.

SRH	MZ & DZ Twin Pairs (N = 892)						MZ Twin Pairs (N = 599)					
	B	SE	q	B	SE	q	B	SE	q	B	SE	q
Sexual Crime	-0.235	0.073	0.004*	-0.235	0.086	0.002*	-0.162	0.087	0.164	-0.186	0.100	0.035*
Violent Crime	0.452	0.452	0.452	-0.059	0.098	0.064	-0.077	0.087	0.324	-0.047	0.118	0.258
Property Crime	0.468	0.468	0.468	-0.025	0.049	0.986	0.017	0.041	0.425	0.002	0.059	0.920
Social Support (SS)	0.154	0.154	0.154	0.001	0.061	0.920	0.019	0.058	0.288	0.009	0.074	0.768
Sexual Crime * SS				-0.005	0.167	0.480				0.093	0.204	0.122
Violent Crime * SS				0.127	0.156	0.029*				-0.066	0.180	0.495
Property Crime * SS				0.049	0.085	0.442				0.030	0.101	0.323
Depression	**B**	**SE**	**q**	**B**	**SE**	**q**	**B**	**SE**	**q**	**B**	**SE**	**q**
Sexual Crime	0.736	0.634	0.102	1.241	0.754	0.014*	0.628	0.634	0.518	0.680	0.738	0.183
Violent Crime	0.363	0.637	0.364	1.021	0.827	0.070	0.558	0.629	0.170	1.078	0.850	0.035*
Property Crime	0.311	0.298	0.461	-0.033	0.435	0.889	-0.067	0.313	0.950	-0.317	0.448	0.714
Social Support (SS)	-2.593	0.415	7.06E-12*	-2.676	0.529	2.52E-06*	-2.071	0.437	3.80E-08*	-2.167	0.559	5.51E-04*
Sexual Crime * SS				-1.712	1.413	0.088				-0.226	1.456	0.164
Violent Crime * SS				-1.437	1.316	0.111				-1.100	1.304	0.124
Property Crime * SS				0.759	0.727	0.380				0.547	0.762	0.714

Note: B = unstandardized coefficient, SE = standard error of the coefficient; * q < 0.05

Again a second analysis was conducted which included the interaction terms of victimization and social support. Among both the MZ and DZ discordant twin pairs together and the MZ discordant twins separately, social support remained significantly associated with lower depression scores. Additionally, we found a main effect of sexual crime on depression after including the interaction terms among the MZ and DZ discordant twin pair analysis (B = 1.241, q = 0.014), but not in the MZ discordant twin pairs. Furthermore, we found a main effect of violent crime on depression in the MZ twin pairs (B = 1.078, q = 0.035). The effect size diminished considerably when compared to the analysis in the general sample (B = 1.707, q = 1,29E-14). It should be noted that these main effects refer to the reference group, which is the group with low social support. Thus, for example, the significant main effect of violent crime on depression in the discordant MZ twin analyses indicated that this association is present in individuals with low social support. The interaction terms were again not significant in any of the discordant twin analyses, indicating that social support did not significantly moderate the impact of victimization on depression after controlling for familial factors.

Discussion

This study aimed to examine the effects of crime victimization on SRH and depression, with a focus on the role of social support as a possible protective factor, in a large sample of Dutch adults. Our general analyses revealed that victimization was significantly associated with poorer health, both SRH as depression, with the exception of victimization of property crime not being associated with SRH. This association was strongest for sexual crimes, followed by violent crimes. These results align with existing literature that highlights the severe impact of sexual victimization on physical health outcomes (e.g. Britt, 2001). Additionally, social support was associated with better health outcomes. These findings align with previous research demonstrating that social support is linked to better mental and physical health (e.g. Harandi, Taghinasab & Nayeri, 2017). However, in the discordant twin analyses, social support was not significantly associated with SRH. This discrepancy suggests that shared genetic and environmental factors confound the relationship between social support and SRH. In contrast, the

negative association with depression persisted, albeit slightly attenuated, in the combined MZ and DZ discordant twin analyses as well as in the MZ discordant twin analyses. These findings underscore the crucial role of social support in mitigating depressive symptoms, even when accounting for shared familial factors. When looking at the moderating effect of social support, our general analyses revealed interaction effects between victimization and social support on both health outcomes, with the exception of the interaction between property crime and depression. The strongest interaction effect was found for sexual crimes, followed by violent crimes. This indicates that individuals with higher social support experienced less negative health effects from sexual crime and violent crime compared to those with lower social support. These results are consistent with prior research that has demonstrated the protective role of social support against the adverse mental health effects of victimization (e.g. Scarpa et al., 2006 ; Holt & Espelage, 2019).

The discordant twin analyses did not indicate that victimization was associated with negative health consequences, with the exception of sexual crime victimization. Sexual crime victimization showed a negative association with SRH among the combined MZ and DZ discordant twin pairs, with a similar effect size to the analyses on the entire sample. However, when looking at the MZ discordant twin analyses, this association was not significant. Furthermore, most interaction effects were not significant in the discordant twin analyses, with the exception of the interaction of violent crime and social support on SRH, in the combined MZ and DZ discordant twin pairs. However, this interaction effect was not significant in the MZ discordant twin pairs, which fully corrects for genetic and shared environmental factors. Furthermore, all other interaction effects observed in the general population failed to emerge in the discordant twin analyses. This suggests that while social support may appear to buffer the negative health impacts of violent crime, this effect is partly due to genetic and shared environmental factors. We must note that one partial explanation for the lack of significance in the discordant twin analyses could be the limited statistical power due to smaller sample sizes especially when analyzing MZ twins separately. As the effect size decreased, but did not disappear entirely, this could indicate that while genetic factors may play a role, they do not fully

explain the relationship. Additionally, one could argue that the unique dynamics of twin relationships might influence the perception and reporting of social support differently compared to the general population. However, previous research found no differences between twins and other siblings regarding social support (Willemsen et al., 2021) nor between MZ and DZ twins (Gonggrijp et al., 2023). Lastly, after adding the interaction terms sexual crime showed a significant impact on SRH and violent crimes with depression in the discordant MZ analyses. This should be interpreted as meaning that for those who experience low social support the experience of sexual and violent crimes negatively impacted their health, even after correcting for shared environmental and genetic confounding. However, since the interaction terms were not significant, it means that within these discordant MZ twins, higher levels of social support did not significantly buffer the impact of victimization on depression or SRH scores after familial factors were accounted for.

Despite the strong design used in this study, several limitations should be acknowledged. Firstly, this study did not account for the severity and frequency of the victimization experience, which can vary significantly and potentially can make a substantial difference for both physical and mental health outcomes. To address this limitation, future research should categorize crime by severity to better comprehend how different levels of victimization affect individuals' well-being. Secondly, it is worth noting that this study relied on self-reported measures, which could result in measurement error in the exposure which may introduce bias in the results (Gustavson et al., 2024). To mitigate this potential bias, future studies could benefit from incorporating objective measures of health outcomes. Thirdly, reverse causality could be present, where early health issues could lead to diminished social networks, further exacerbating health outcomes. In contrast, those without such early challenges may experience more robust social support, offering them better protection against the negative effects of victimization. Lastly, it is possible that the victimization of one member of a twin pair also has an impact on the health of the other. This spillover effect could arise due to the close emotional bond and shared environment of twins, where the stress and trauma experienced by one twin could adversely affect the psychological and physical health of the other. Future

studies should explore this dynamic to better understand the full scope of victimization's impact within twin pairs.

In conclusion, this study underscores the clear association of crime victimization, particularly victimization of sexual and violent crimes, with SRH and depression. While social support emerged as a protective factor, its moderating effects on health outcomes appear to be confounded by familial factors. This indicates that when genetic and shared environmental factors are accounted for, the protective effects of social support following victimization may not be as robust as previously thought. Social support in itself, however, remains to have a positive effect on health, even after controlling for unmeasured familial factors. These findings highlight the complexity of the relationship between victimization, social support, and health outcomes, and underscore the importance of considering familial influences in future research to better understand these dynamics.

Chapter 6.

Negative Life Events and Epigenetic Aging

Abstract

We aimed to understand the long-term impact of negative life events (NLE) on epigenetic aging in 1,783 adults from the Netherlands Twin Register, analyzing five epigenetic biomarkers (Hannum, Horvath, PhenoAge, GrimAge, DunedinPACE) and a series of NLE, including victimization and economic hardship. In population-level analyses, associations between a higher number of NLE (particularly financial adversities, sexual crimes, and job loss) were seen for the GrimAge biomarker. The association between the number of NLE and financial problems and epigenetic age acceleration measured by the GrimAge biomarker persisted after adjusting for BMI, smoking, and white blood cell counts. In monozygotic twin pairs discordant for NLE (263 pairs) the associations were diminished, indicating that the population associations may be confounded by shared familial (genetic and environmental) factors. These findings underscore the intricate link between environmental stressors and biological aging, stressing the need for comprehensive studies considering both genetic and environmental influences.

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Negative Life Events and Epigenetic Aging

Negative life events influence numerous aspects of lives of individuals who experience them. Extensive prior research has consistently linked the experience of negative life events to negative life outcomes across domains such as relationships, employment, and elevated risks of health problems, including mental health problems, poor cognitive functioning, cardiovascular disease, gastrointestinal complications, musculoskeletal problems, reproductive challenges, compromised immune function, and disruptions in the endocrine system (Monaghan & Haussmann, 2015; och Dag et al., 2020; Patton et al., 2003; Young & Schieman, 2012). Previous research also revealed a connection between negative life events and premature mortality. For example, Pridemore and Berg (2017) found that men who had recently undergone violence have 2.6 times higher odds of facing premature death in comparison to those who had not experienced this. Research into adverse childhood experiences also revealed profound and enduring effects on lifespan: a study by Brown et al. (2009) found that individuals who have endured six or more of such experiences typically have a life expectancy nearly 20 years shorter than those without such adversities.

Given the substantial evidence linking negative life events to a range of poor life outcomes and health, we ask how we may understand the underlying biological mechanisms that mediate these effects. While multiple factors contribute to the complex interplay between exposure to negative life events and health outcomes, one area gathering significant attention is epigenetics. Epigenetic changes to the DNA code affect gene expression, without changing the code itself. DNA methylation is a process where a methyl group is added to DNA, altering gene activity without changing the DNA sequence itself, and influencing the way genes are expressed. In large-scale epidemiological studies, epigenetic changes can be measured quantitively by differential DNA methylation when a methyl group is added to a CpG dinucleotide. Such changes can be assessed on arrays with 400.000 to ~900.000 markers. Based on array methylation data, multiple markers of biological aging have been proposed. Their development and definition are through algorithms that estimate an individual's 'DNA

methylation age' based on the methylation levels at specific CpG sites in the DNA (Raffington & Belsky, 2022). The deviation of DNA methylation age from chronological age, referred to as "epigenetic age acceleration", has been linked to increased mortality risk (Marioni, Shah, McRae, Chen, et al., 2015) and a range of adverse health outcomes, such as cognitive impairment and poor physical and cognitive fitness (Levine et al., 2015; Marioni, Shah, McRae, Ritchie, et al., 2015).

The first-generation epigenetic age acceleration measures included the Hannum and Horvath 'clocks' and were designed to compare the biological age of older individuals with that of younger ones. These early epigenetic biomarkers utilized machine learning to estimate a person's chronological age based on DNA samples collected at a specific ages. While these first-generation biomarkers showed moderate effectiveness in predicting mortality, they predicted less well when forecasting other age-related conditions, including diseases, disability, and declines in physiological and functional capacities (Bell et al., 2019; Hannum et al., 2013; Horvath, 2013). development of next-generation epigenetic markers like PhenoAge and GrimAge was a two-step process aimed at predicting an individual's lifespan using survival analysis. Initially, PhenoAge was created by correlating physiological markers with remaining lifespan, generating a score based on these markers. The process then extended to incorporate DNA methylation data, refining the PhenoAge score to a DNA methylation-based version. GrimAge, while also employing machine learning, further includes factors like age, sex, and smoking history, offering a more comprehensive assessment of physiological aging. Both biomarkers have proven to be more accurate in predicting morbidity and mortality compared to the first-generation biomarkers (Levine et al., 2015). Recently, a pace of aging measure has emerged, the DunedinPACE. DunedinPACE evaluates the rate of aging by analyzing changes over age in multiple physiological systems. This algorithm was trained to integrate information from a range of biomarkers across cardiovascular, metabolic, renal, immune, dental, and pulmonary functions. By assessing changes over time, DunedinPACE can estimate the rate at which these systems are aging in each individual. Thus, while the Hannum, Horvath, PhenoAge, and GrimAge are interpreted as

biological age in years, DunedinPACE values represent rates of aging (Belsky et al., 2022; Raffington & Belsky, 2022). Table 6.1 provides an overview of the epigenetic biomarkers we will consider, with the criterion used, information about the discovery sample, and interpretation of the measure's values.

A handful of studies examined the relationship between exposure to adverse childhood life events and biological aging. For instance, Sumner et al. (2023) collected saliva samples for DNA isolation in 161 participants aged 8 to 16 years and discovered that experiencing everyday stressful life events during adolescence was associated with accelerated epigenetic aging as indexed by the Horvath measure. Joshi et al. (2023) conducted a study involving 1445 individuals aged 45 to 85 from whom blood samples were collected. They explored second-generation measures and found that childhood exposure to parental separation or divorce and emotional abuse was linked to higher

Table 6.1. Description of three generations of biological aging measurements.

Measure	Training Tissue	Training Sample	Age	Predicted trait
		First Generation: Chronological age predictors		
Horvath	51 healthy tissues and cell types	7844 Adults across 82 different datasets across entire lifespan	0-100	Chronological age predicted by DNA methylation
Hannum	Whole blood	482 adult volunteers at UC San Diego, University of Southern California, and West China Hospital.	19-101	
		Second Generation: Mortality risk predictors		
PhenoAge	Whole blood	9926 adults from the InCHIANTI Study	21-100	Blood-chemistry PhenoAge
GrimAge	Whole blood	6935 Adults from the Framingham Heart Study Offspring Cohort.	53-73	Mortality risk
		Third generation: Pace of Aging		
DunedinPACE	Whole Blood	1037 participants from the Dunedin Study 1972 1973 birth cohort.	Measured at 26, 32, 38 and 45 years	Physiological decline experienced per 1 year of calendar time.

GrimAge acceleration but not to PhenoAge acceleration in later life. Raffington et al. (2021) examined 600 children and adolescents aged 8 to 18 in the Texas Twin Project, measuring saliva DNA methylation and socioeconomic circumstances. Children from more disadvantaged families and neighborhoods exhibited a faster pace of aging as measured by DunedinPACE. Kim et al. (2023) examined 895 adults (mean age 40.4) and 5 years later followed up nearly this entire group. Their research revealed that individuals who had experienced a higher number of adverse childhood experiences displayed accelerated biological aging for the PhenoAge, GrimAge, and DunedinPACE. This effect persisted into midlife and earlier adulthood, even after accounting for demographic, behavioral, and socioeconomic variables.

Research on negative life events during adulthood has often focused on Post-Traumatic Stress Disorder (PTSD), with conflicting findings. For instance, Wolf et al. (2019) reported that PTSD was linked to faster aging based on the Horvath but not the Hannum measure, while Oblak et al. (2021) found an age acceleration for the Hannum, but deceleration for the Horvath measure. Wang et al. (2023) conducted a cross-sectional co-twin control study design with DZ and MZ twins discordant for current PTSD to control for shared genetic and other familial factors. They found that twins with PTSD exhibited significantly advanced DNA methylation age acceleration compared to their twin brothers without PTSD across several biomarkers — Horvath, Hannum, and PhenoAge — but not GrimAge. These findings indicated that, across most measures of DNA methylation age acceleration, twins with current PTSD were ‘epigenetically older’ by an estimated 1.6 to 2.7 years of biological age than their unaffected twin siblings and suggest that the effect is not influenced by genetic or shared environmental confounding. In contrast, Yang et al. (2021) and Katrinli et al. (2023) found an association of PTSD with GrimAge acceleration. The variability in findings across different measures of DNA methylation age acceleration likely reflects the distinct biological processes captured by each epigenetic clock. Adverse childhood experiences appear to be more consistently associated with second- and third generation biomarkers, such as PhenoAge, GrimAge, and DunedinPACE, which are more comprehensive in their

assessments. However, findings regarding traumatic stress disorder during adulthood and accelerated aging are less consistent. The differences in associations across studies might stem from sample characteristics, such as age, socioeconomic background, and the specific type and timing of the adverse experiences. Additionally, variations in how PTSD and other stress exposures are measured—whether by self-report or clinical diagnosis — or the timing of PTSD diagnosis relative to DNA measurement, and methodological variations could influence the relationship between stress and biological aging. This variability underscores the need for further research to clarify how different forms of life stress influence specific biological aging markers and the mechanisms driving these associations.

The Current Study

We aim to contribute to the existing literature by investigating the association between negative life events and blood-cell-derived epigenetic age acceleration in adulthood in a large population-based sample of twin families from the Netherlands Twin Register (N=1,808, including 421 monozygotic twin pairs). Most previous research has centered on childhood adversity or traumatic events in the context of PTSD, or focused on a restricted subset of epigenetic biomarkers. Our study enriches the existing literature by examining a broad spectrum of negative life events, ranging from crime victimization and financial troubles to losing a loved one in a population-based cohort of adults, and look at the five most widely researched biomarkers: Hannum, Horvath, PhenoAge, GrimAge, and DunedinPACE. In our study, we initially explored the link between the total number of negative life events and epigenetic age acceleration in all participants. Next, we investigated the association between specific life events and epigenetic age acceleration. Finally, we conducted within-pair analyses in monozygotic twin pairs who were discordant for life events. This part of the study focused on comparing epigenetic age acceleration between twins who experienced a different number of negative life events. This analysis controls for shared environmental and genetic confounding (Gesell, 1942; Gonggrijp et al., 2023; Wang et al., 2023) and aims to elucidate the direct impact of negative life events on epigenetic aging, independent of genetic and shared environmental factors. To the best of our knowledge, this research is the first to

implement a discordant twin analysis concerning epigenetic biomarkers and negative life events (other than PTSD). By examining the relationship between epigenetic age and negative life events, this research seeks to shed light on the underlying mechanisms linking negative life events to negative health outcomes.

Methods

Cohort Description

Data were collected from participants from the Netherlands Twin Register (NTR). Respondents fill out surveys on health and lifestyle every two to three years. Full details about data collection have been reported previously (Distel et al., 2011; Ligthart et al., 2019). DNA was collected from buccal cells and whole blood as part of multiple projects. For the current paper, we analyzed DNA methylation measured in whole blood collected in the NTR-Biobank study, conducted in 2004–2008 or 2010–2011, (Sirota et al., 2015; Willemsen et al., 2010). The 450kDNA methylation array data were generated for all samples, regardless of year of sample collection, in one batch.

The selection of participants is detailed in Figure 6.1. Good quality whole blood DNA methylation data were available for 3,055 participants. Outliers of the epigenetic biomarkers were removed from the dataset (N_{AARH} = 68, N_{IEAA} = 97, $N_{PhenoAge}$ = 194, $N_{GrimAge}$ = 127, $N_{DuneDinPACE}$ = 68), none of the participants had outliers for all epigenetic biomarkers. Participants were excluded from the analytic sample if they had missing data on the covariates (N_{BMI} = 16, $N_{smoking}$ = 9, N_{WB} = 76) or if data on life events were missing (N = 949). Among the remaining 2,005 participants, there were 556 controls who had not experienced any of the life events. Among 1,449 participants who experienced at least one of the life events, 222 were excluded because they reported that these life event(s) occurred prior to DNA collection. The other 1,227 participants were included in the total sample as cases. The total sample therefore consisted of 1,783 individuals with data on life events and epigenetic biomarkers, including 1,649 twins, 12 siblings, 63 fathers, 57 mothers and 2 spouses of twins. For the sensitivity analyses, which adjusted for educational attainment (EA), participants with missing data on EA variable were excluded from the total sample (N_{AE} = 304).

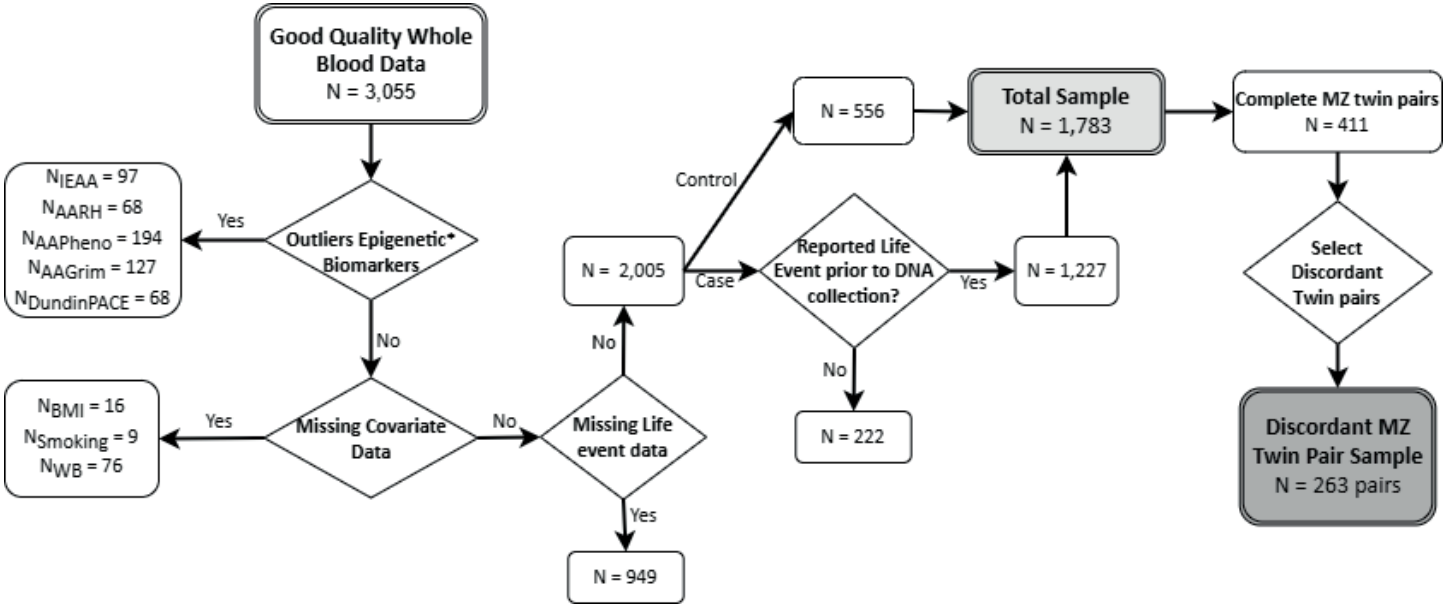


Figure 6.1. Flowchart of Data Selection. AARH = Hannum Age Acceleration, IEAA = Intrinsic Epigenetic Age Acceleration, AAPheno = PhenoAge Acceleration, AAGrim = GrimAge acceleration, WB = Whole Blood. Control depict participants who did not experience any life events. * None of the participants had outliers for all biomarkers.

Ethics

Written informed consent was obtained from all participants. The study was approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Centre, Amsterdam, an Institutional Review Board certified by the U.S. Office of Human Research Protections (IRB number IRB00002991 under Federal-wide Assurance- FWA00017598; IRB/institute codes, NTR 03-180).

DNA Collection

DNA Methylation

DNA methylation was assessed with the Infinium HumanMethylation450 BeadChip Kit (Illumina, San Diego, CA, USA) by the Human Genotyping facility (HugeF) of ErasmusMC, the Netherlands (http://www.glimdna.org/) as part of the Biobank-based Integrative Omics Study (BIOS) consortium (Ruth et al., 2021). DNA methylation measurements have been described previously (Ruth et al., 2021; Van Dongen et al., 2016). Genomic DNA (500ng) from whole blood underwent bisulfite treatment with the Zymo EZ DNA Methylation kit (Zymo Research Corp, Irvine, CA, USA), and 4 µl of bisulfite-converted DNA was measured on the Illumina 450k array following the manufacturer's protocol. A number of sample- and probe-level quality checks and sample identity checks were performed, as described in detail previously (Van Dongen et al., 2016). In short, sample-level QC was conducted with the assistance of MethylAid (Van Iterson et al., 2014). Probes were set to missing in a sample if they had an intensity value of exactly zero, a detection p>.01, or a bead count of<3. After these steps, probes that failed based on the above criteria in >5% of the samples were excluded from all samples (only probes with a success rate≥ 0.95 were retained). The methylation data were normalized with functional normalization (Fortin et al., 2014).

DNA-methylation biomarker of biological aging

DNA methylation age acceleration measures of Hannum, Horvath, PhenoAge, and GrimAge were computed through the Horvath epigenetic age calculator (https://dnamage.genetics.ucla.edu/) and included the following outputs:

1. Hannum age acceleration—"AgeAccelerationResidualHannum" (AARH),

2. Intrinsic epigenetic age acceleration; the residual resulting from regressing the DNAm age estimate from Horvath on chronological age and blood cell count estimates.—"IEAA",
3. PhenoAge acceleration—"AgeAccelPheno" (AAPheno),
4. GrimAge acceleration—"AgeAccelGrim" (AAGrim)

DunedinPACE was calculated based on code accessible on GitHub (https://github.com/danbelsky/DunedinPACE). For each epigenetic biomarker, outliers were assessed and datapoints were removed when they were 3 times above or below the interquartile range (N_{IEAA} = 77, N_{AARH} = 57, $N_{AAPheno}$ = 164, N_{AAGrim} = 118, $N_{DundinPACE}$ = 59). The age acceleration values of the Hannum, Horvath, PhenoAge, and GrimAge biomarkers are on the same scale; they are expressed as the difference (in units of years) in estimated biological age and chronological. For instance, a value of 0 means that a person's biological age is equal to their chronological age while values greater than 0 are interpreted as accelerated ageing and values smaller than 0 as decelerated aging. In contrast, the DunedinPACE algorithm does not estimate biological age (in units of years) but pace of ageing; a measure of how fast someone is ageing at the moment of sample collection. It is scaled such that a value of 1 corresponds to people who gain 1 year in biological age per year of chronological age. Values greater than 1 are interpreted as accelerated biological aging and values smaller than 1 are interpreted as decelerated biological aging.

Life Events

NTR administered a Dutch life event scale, the "*Schokverwerkings Inventarisatie Lijst*" (Middeldorp et al., 2008; van der Velden et al., 2021) in the 2009 survey. Participants were asked about traffic accident, violent assault, sexual assault, robbery, death of a spouse or child, serious illness or injury of self, spouse or child, job loss, and financial problems, with response categories "never experienced", "less than 1 year ago", "1–5 years ago" and "more than 5 years ago". For divorce or break-up of a relationship equivalent to marriage, the response category was yes or no. All responses were recoded into binary variables indicating whether an individual had ever experienced each particular event prior to DNA collection, with 'yes' or 'no' as possible responses. The prevalence of each

type of life event is given in Table 2. For our analyses, we also computed a sum score reflecting the total number of negative life events encountered by a participant, ranging from 0 to 9 as no participant had experienced all twelve life events.

Covariates

To adjust for technical variation, array row and bisulfite plate (dummy-coding) were included as covariates as were sex and chronological age (Krieger et al., 2023), measured at time of blood draw. BMI was computed based on reported weight and height (kg/m2) obtained at blood draw. Smoking status was classified as non-smoker (coded as 0), former-smoker (coded as 1), and current-smoker (coded as 2) obtained at blood draw.
After blood collection, cell counts were measured in fresh material by complete cell count method. The following subtypes of white blood cells were assessed: neutrophils, lymphocytes, monocytes, eosinophils, and basophils (Bochao Danae Lin et al., 2017; Bochao D Lin et al., 2017; Willemsen et al., 2010). Lymphocyte and neutrophil percentages were strongly negatively correlated ($r=-0.93$, $p<0.001$). Of these two white blood cell subtypes, the percentage of neutrophils showed the strongest correlation with DNA methylation levels (as evidenced by the correlation with PCs from the raw genome-wide methylation data). Basophil percentage showed little variation between subjects, with a large number of subjects (90,9%) having <1% of basophils. Therefore, the percentages of neutrophils, monocytes, and eosinophils were included as covariates in sensitivity analyses to adjust for inter-individual variation in white blood cell proportions.

Educational attainment (EA) was included as a categorical covariate in the sensitivity analyses. EA was assessed as the highest level of education completed at the time of data collection based on survey data available for the participants from age 25 onwards. Participants below the age of 25, who possibly had not yet completed their education, were excluded from the sensitivity analyses. The answer categories were recoded into seven categories of completed EA: 1 = primary school, 2 = lower vocational schooling, 3 = lower secondary schooling (general), 4 = intermediate vocational schooling, 5 = intermediate/higher secondary schooling (general), 6 = higher vocational schooling, 7 =

university. If participants had not completed the highest schooling EA , then one lower level of EA was defined

Data Availability

The HumanMethylation450 BeadChip data from the NTR are available as part of the Biobank-based Integrative Omics Studies (BIOS) Consortium in the European Genome-phenome Archive (EGA), under the accession code EGAD00010000887. They are also available upon request via the BBMRI-NL BIOS consortium (https://www.bbmri.nl/acquisition-use-analyze/bios). All NTR data can be requested by researchers (https://ntr-data-request.psy.vu.nl/).

Statistical Analysis.

Associations between experiencing negative life events and epigenetic age acceleration at the population level were tested in R in generalized estimating equation (GEE) models taking clustering within families into account. First, we assessed the impact of the total number of negative life events experienced by participants, creating a sum score ranging from 0 (no life events experienced) to 9. We recognize that this approach does not take into account that some life events may be more severe than others and may have more impact on epigenetic age acceleration. Therefore, we also analyzed the effect of individual life events, which allows regression coefficients to vary across the different life events. in one model, with each coded as 0 (not experienced) or 1 (experienced life event). Next, to address overlapping life events, we conducted separate analyses for each life event, comparing participants who had not experienced any of the twelve negative life events to those who experienced specific ones. GEE models were fitted with the R package GEEpack, with the following specifications: Gaussian link function, 100 iterations, and the 'exchangeable' option to account for the correlation structure within families. For each of these analyses, we considered three models. In the primary model, we corrected for chronological age (as previously recommended by Krieger et al., 2023), sex, and array row and bisulfite plate only. In the second model, we additionally adjusted for smoking, BMI and white blood cell proportions, to examine whether the associations between negative life events and epigenetic aging might be driven by lifestyle, blood cell

composition. We note that some (but not all) of the epigenetic biomarkers already correct for (estimated) white blood cell composition by design to derive a measure of age acceleration that is approximately independent of cellular composition and that one biomarker (Hannum – designed to represent a marker of aging of the immune system) explicitly incorporates estimated white blood cell composition in the calculation of biological age. Lastly, sensitivity analyses were performed in a subsample which additionally corrected for EA. To assess the proportion of variance explained (R^2) in each model, we calculated an R^2-like measure, as GEE models do not inherently provide an R^2 value, as follows:

$$R^2_{GEE} = 1 - \frac{\Sigma\,(y - \widehat{y})^2}{\Sigma\,(y - \overline{y})^2}$$

where y represents the observed values of epigenetic age acceleration, $\hat{y}$ represents the values predicted by the GEE model, and $\bar{y}$ is the mean of the observed values.

After conducting the population-level analyses, we examine the associations between the number of negative life events and epigenetic aging in discordant monozygotic twin pairs. Due to the small numbers of discordant monozygotic twin pairs for specific life events, such as loss of a child or partner, discordant twin pair analyses were not conducted separately for the specific life events. We defined the number of life events for both twins within monozygotic twin pairs, where pairs in which the twins did not experience the same number of life events were classified as discordant. For the within-twin pair analyses, the same three models were considered, without correction for sex and age, as these are the same within MZ twin pairs. These analyses were done with fixed effects regression in R (Gonggrijp et al., 2023). We also calculated the R^2 (within R^2) for each model which provides an estimate of the variation in epigenetic aging that can be attributed to differences in the number of life event exposure within the twin pairs. Given the discordant twin design and the sample size of 263 pairs, the study was well-powered to detect associations between the number of negative life events and epigenetic age acceleration. Previous research estimated that ~25 MZ pairs are needed to achieve 80% power to detect a mean difference of 8% in DNA methylation levels at a significance

threshold of p = 0.05 (Tsai & Bell, 2015). While our focus is on epigenetic clocks rather than individual methylation sites, our larger sample size provides a strong foundation for detecting differences in epigenetic aging, making our findings robust and informative for future research.

Correction for multiple testing was done by Bonferroni correction based on the number of independent tests (α = 0.05/N independent tests). To estimate the number of independent variables in the correlation matrices of the dependent and independent variables, we employed Matrix Spectral Decomposition (Nyholt, 2004) in R. A tetrachoric correlation matrix encompassing all 12 life events and a Spearman's correlation matrix for the 5 epigenetic biomarkers was used as inputs (see Supplementary Table 6.1). We identified eight independent dimensions related to life events and three pertaining to the epigenetic biomarkers. This resulted in a cumulative total of 8*3 = 24 independent tests, leading to an adjusted alpha level of 0.002. Corresponding confidence intervals in the figures were adjusted to reflect this alpha level, thereby providing 99.8% confidence intervals for estimates.

Results

Descriptive Statistics

Table 6.2 presents the prevalence of various life with being the victim of theft emerging as the most common life event, experienced by 25.69% of the entire sample. This was closely followed by serious illness at 20.69%. The death of a partner and the death of a child had the lowest prevalence rates, 2.36% and 1.41% respectively. Only 563 (31.65%) participants did not experience any of the measured life events. Figure 6.2 presents a visualization of all life events experienced by participants, highlighting the most common combinations of events. For instance, while a significant number of participants reported theft as an isolated event (N=109), others have experienced theft concurrently with other life events (e.g., 39 times with traffic accidents, 28 times with serious illness, and 28 times with job loss). Figure 6.2 includes only those groups or combinations of events where at least 10 individuals are represented. A full visualization that includes all reported combinations of life events, regardless of their frequency can

be found online (https://github.com/bmagonggrijp/InvisibleScars). The intricate web of intersections in the matrix section of both Figure 6.2 and Supplementary Figure 6.1 indicates that a majority of participants experienced more than one negative life event (N=790), rather than a single incident. The live events sum score, representing the total number of different life events encountered, had an average of 1.32 and a SD of 1.34.

Table 6.3 displays the descriptive statistics for the epigenetic biomarkers, white blood cell counts, BMI, smoking status, and EA. The mean age of the participants was 37.69 (SD = 13.27), and the majority of the participants was female (69.45%).

Table 6.2. Prevalence of experiencing negative life events.

Negative Life Event	**Not experienced**		**Experienced**	
	N	**%**	**N**	**%**
Accident	1427	80.03%	356	19.97%
Violent Crime	1677	94.05%	106	5.95%
Sexual Crime	1654	92.77%	129	7.23%
Theft	1331	74.65%	452	25.35%
Death of Partner	1742	97.70%	41	2.30%
Death of Child	1759	98.65%	24	1.35%
Illness Partner	1605	90.02%	178	9.98%
Illness Child	1626	91.19%	157	8.81%
Illness Self	1420	79.64%	363	20.36%
Job loss	1490	83.57%	293	16.43%
Financial Problems	1624	91.08%	159	8.92%
End of Relationship	1611	90.35%	172	9.65%
Sum Score	**Mean**	**SD**	**Min**	**Max**
Negative Life Events	1.363	1.390	0	9

Note: Those who experienced a life event can overlap. Sum Score depicts the total number of different events experienced.

Table 6.3. Descriptive statistics of the epigenetic biomarkers, chronological age, white blood cell counts, sex, BMI, and smoking status.

	N	Min	Max	M	SD
Chronological Age*	1783	17.60	79.60	37.67	13.18
AARH	1744	-19.715	41.910	-0.109	3.779
IEAA	1729	-25.870	29.777	0.017	4.016
AAPheno	1667	-30.226	40.361	-0.124	5.243
AAGrim	1708	-10.457	15.957	-0.338	3.553
DunedinPace	1741	0.616	1.391	0.969	0.106
White Blood Cells					
Neutrophils %	1783	1.800	84.300	52.427	9.130
Monocytes %	1783	1.000	27.500	8.407	2.169
Eosinophils %	1783	0	60.100	3.100	2.373
BMI	1783	14.491	48.895	24.310	3.923
	N	**%**			
Sex (1= male)	531	29.78			
Smoking Status					
Never-Smoker	1041	58.38			
Former-Smoker	417	23.39			
Current-Smoker	325	18.23			
Educational Attainment					
Primary Education	31	2.10			
Lower Vocational Education	103	6.96			
Lower Secondary Education	97	6.56			
Intermediate Vocational Education	425	28.74			
General Secondary Education	72	4.87			
Higher Vocational Education	423	28.60			
University	328	22.18			

Note: * Age at time of blood collection; AARH = Age Acceleration Residual Hannum, IEAA = Intrinsic Epigenetic Age Acceleration, AAPheno = Age Acceleration PhenoAge, AAGrim = Age Acceleration Grim Age, DunedinPACE = Dunedin Pace of Ageing

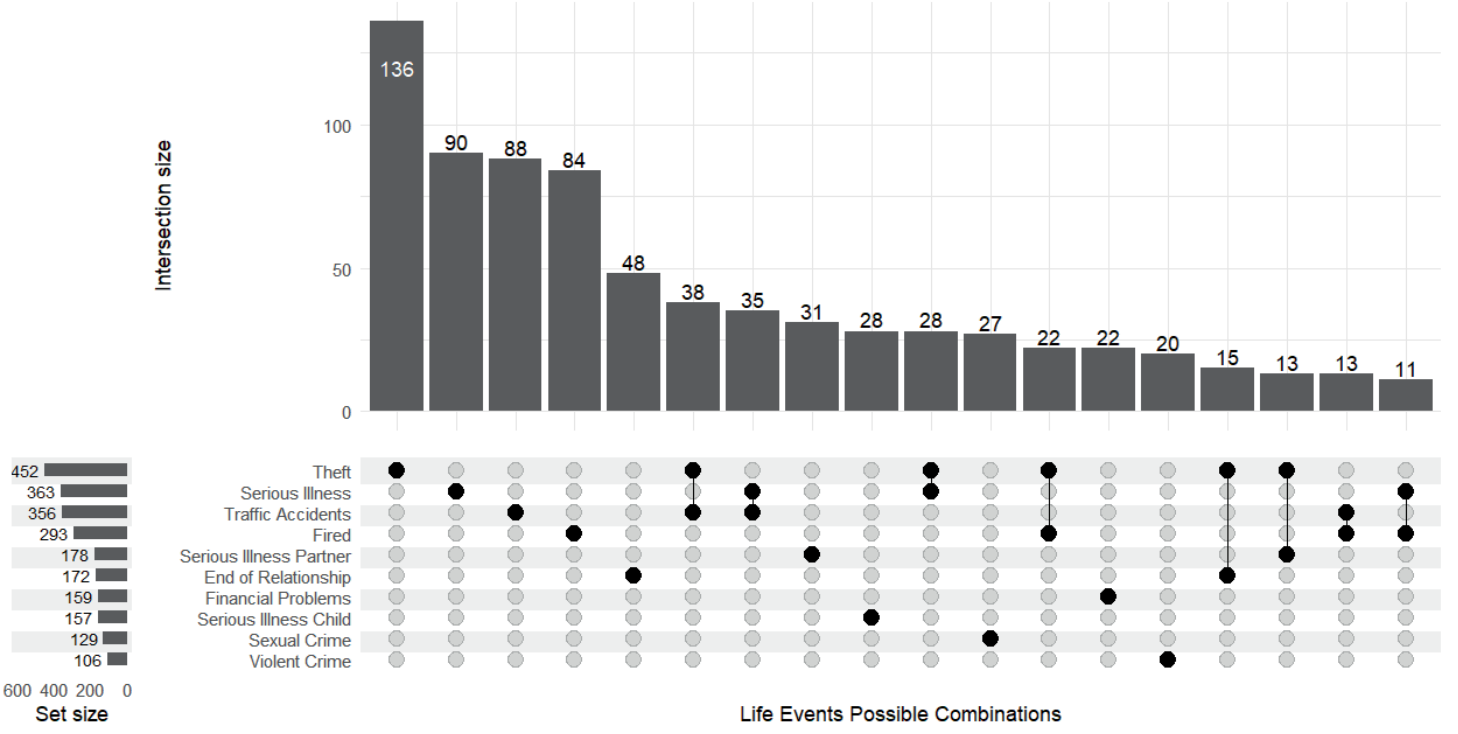


Figure 6.2. Visualization of Single and Multiple Experienced Life Events. The horizontal bars show how often each life event occurs in the total sample (e.g., 452 thefts). The first five vertical bars show that respectively 136, 90, 88, 84, and 48 respondents only experienced a single life event, i.e., theft, serious illness, traffic accidents, being fired, and end of serious relationship. The fifth and sixth vertical bars show the two most common combinations of life events: 38 respondents experienced both theft and traffic accidents, and 35 respondents experienced serious illness and traffic accidents. Only combinations with 10 participants or more are depicted in the graph.

Population Analyses

Prior to the population analyses, a GEE was conducted to look at the associations between the epigenetic biomarkers and the covariates and among the life events and the covariates (see Supplementary Tables 6.2 and 6.3). Almost all covariates showed a significant relationship with the 5 epigenetic biomarkers. For example, smoking was associated with epigenetic age acceleration for the GrimAge, and DunedinPACE biomarkers. Sex differences were observed for the Hannum and GrimAge biomarkers, with men showing an increased acceleration compared to women. These findings underscore the importance of considering factors like smoking and sex in the analysis of epigenetic aging. BMI and white blood cell counts were not associated with negative life events. However, sex was associated with the sexual crimes and age was associated with multiple negative life events.

Results of the first analyses, in which associations were adjusted for chronological age, sex, and array row and bisulfite plate , are outlined in Table 6.4. The Hannum, Horvath, PhenoAge, and DunedinPACE did not exhibit significant associations with the total number of negative life events, or any of the specific life events when the life events were considered simultaneously in the model. In contrast, the upper part of Table 6.4 shows that the GrimAge biomarker demonstrated a significant increase in epigenetic aging related to the total number of experienced life events B = 0.268 p = 2.50E-04.). The regression coefficient of GrimAge implies that each additional life event experienced is associated with an acceleration of biological aging by almost 0.3 years. Therefore, if an individual has experienced four life events, this corresponds to 0.268 * 4 = 1.07 additional years of biological aging in comparison to someone who has not experienced any of the life events [2]. The middle part of Table 4 shows the results of the subsequent analyses in which the associations with all negative life events were estimated simultaneously. These analyses revealed that only financial adversities were linked to an age

[2] *In sensitivity analyses, we included the squared z-score of the sum score of life events in the model to test for possible non-linear effects. The squared z-score of the life events sum score was not significant.*

acceleration of approximately 1.4 years in GrimAge (B = 1.391, p = 7.60E-05) when all life events were considered concurrently.

We also conducted additional GEE analyses in which respondents who experienced a particular life event were compared to a control group of respondents who reported no life events. This approach was intended to isolate the impact of each specific life event. Results are shown in the lower part of Table 6.4. These analyses reinforced the association between financial adversities and an acceleration in GrimAge (B =1.650, p =2.90E-06) and further identified significant associations for sexual crimes (B = 1.133 p = 0.002) and job loss (B = 0.867, p = 0.001). The DunedinPACE biomarker similarly showed acceleration for financial problems (B = 0.026, p = 0.002). Financial adversities and experiencing sexual crimes were thus associated with approximately 1.7 and 1.1 years of age acceleration for the GrimAge biomarker, and financial adversities with an increased pace of aging of 0.03 years, roughly 10 days, per calendar year to DunedinPACE.

Table 6.5 presents the outcomes of the second model, additionally adjusted for BMI, smoking and white blood cell count. No new significant associations emerged after these correction. The regression coefficient slightly increased for the total number of life events and the Grimage biomarker (B = 0.285, p = 3.19 E-05). When considering the life events simultaneously, the regression was reduced for experiencing financial problems and the GrimAge biomarker, (B = 0.875, p = 0.001). In the model that considered the life events separately, a notable change was observed with the DunedinPACE biomarker. After accounting for BMI, smoking and white blood cell count, the previously significant association of financial adversities and the DunedinPACE lost their statistical significance, and effect sizes were reduced by half. This suggests that lifestyle factors such as BMI and smoking significantly impact the association observed with this particular biomarker. In the case of the GrimAge biomarker, after incorporating BMI and smoking as covariates, the age acceleration link with experiencing sexual crimes and job loss went away. However, financial problems continued to show an acceleration regarding the GrimAge biomarker (B= 1.002, p = 2.32E-04).

Sensitivity analyses, which took into account chronological age, sex, array row and bisulfite plate, lifestyle factors, white blood cell counts, and EA can be found in Supplementary Table 6.4. This led to the attenuation of several associations. GrimAge continued to demonstrate significant associations, indicative of its robustness across various model specifications. Table 6.5 shows that the total number of life effects was associated with an increase in epigenetic aging as per the GrimAge biomarker (B =0.302, p = 2.20E-05). For financial problems the association with the GrimAge biomarker was not statistically significant when considering the life events together. Interestingly however, the regression coefficient was only slightly reduced compared to Model 1 and Model 2 (B = 0.807, p = 0.004) Notably, the lower part of Table 6.5, which depicts the results of the model which considers the life events separately, shows that financial difficulties continued to exhibit the strongest association with age acceleration, contributing to an increase of 0.949 (p = 9.23E-04) years in epigenetic age in comparison to those who did not experience any of the life events.

The explained variance of each model reveals notable patterns. In the second model, which included lifestyle factors, white blood cell counts, and chronological age, there was an increase in R^2, compared to the first model. In contrast, the third model, which additionally incorporated EA, showed only a modest increase in explained variance compared to the jump observed from Model 1 to Model 2. This shows that while smoking, BMI, and white blood cell counts contributed significantly to explaining variance in epigenetic age, the inclusion of EA added only a relatively small amount of additional explained variance.

Discordant Twin Pair Analyses

Supplementary Table 6.5 gives the numbers of concordant and discordant MZ twin pairs for the number of life events. In the group of MZ twin pairs, we observed 148 (36.01%) pairs that were concordant for the total number of life events and 263 (63.99%) pairs that were discordant. Following the population analyses, discordant MZ twin pair analyses were conducted for the epigenetic biomarkers and the total number of life events in MZ discordant pairs. Full results of the discordant twin analyses can be found in

Supplementary Table 6.6. These analyses showed associations between the total number of life events and age acceleration for the biomarkers Horvath, GrimAge and DunedinPACE, while Hannum and PhenoAge showed a small deceleration in all of the models.. However, none of these associations were significant. Figure 6.3 illustrates the comparison between the population analyses and the discordant twin analyses for the GrimAge biomarker, showcasing results with the adjusted 99.8% confidence intervals due to the adjusted alpha level of 0.002. It is clear that the associations observed in the population sample in all models were reduced by more than half in the MZ twin analyses, suggesting genetic and/or shared environmental confounding.

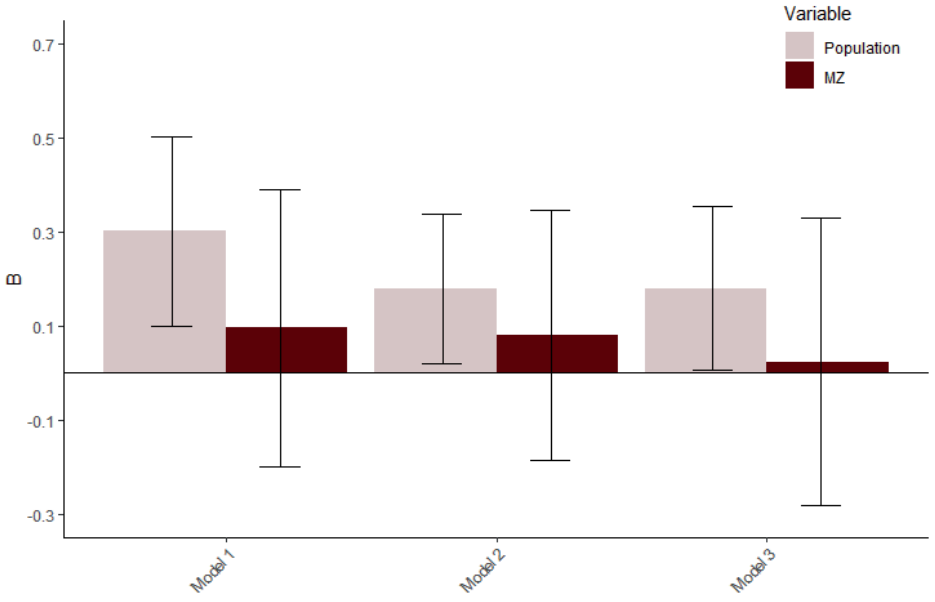


Figure 6.3. Associations of GrimAge with Total Number of Life Events: Population vs. Discordant MZ Twin Analyses for the Different Models. Model 1 Corrects for Age, Sex, and Technical Covariates. Model 2 Additionally Adjusts for BMI, Smoking, and White Blood Cell Count, and Model 3 Additionally Adjusts for Educational Attainment. 99.8% CI (p<.002).

Table 6.4. GEE Analyses Investigating the Associations Between Epigenetic Aging and All Negative Life Events Estimated both *Simultaneously* and *Separately*, adjusted for Age, Sex, and Technical Covariates.

	Hannum			IEAA			PhenoAge			GrimAge			DunedinPACE		
Life events	**B**	**p**	**R^2**	**B**	**p**	**R^2**	**B**	**p**	**R^2**	**B**	**p**	**R^2**	**B**	**p**	**R^2**
Any Life event	0.036	0.611	0.073	0.041	0.569	0.036	0.060	0.528	0.192	**0.268**	**2.50E-04**	**0.197**	0.004	0.030	0.299
Life Events Considered Simultaneously															
Life events	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**
Accident	0.293	0.188		0.244	0.239		0.402	0.187		0.183	0.355		0.004	0.498	
Violent Crime	0.253	0.590		0.671	0.074		0.019	0.975		0.037	0.921		-0.020	0.060	
Sexual Crime	-0.563	0.103		-0.564	0.060		-0.661	0.199		0.881	0.013		0.021	0.026	
Theft	-0.148	0.454		0.050	0.800		-0.153	0.580		-0.295	0.094		-0.012	0.013	
Death of Partner	0.118	0.826		0.556	0.321		0.890	0.311		0.712	0.345		0.019	0.221	
Death of Child	-0.542	0.540		1.208	0.104		0.485	0.680		0.289	0.759		-0.003	0.872	
Illness of Partner	-0.168	0.608	0.077	-0.540	0.128	0.041	-0.196	0.681	0.051	0.165	0.611	0.102	0.006	0.515	0.154
Illness of Child	0.155	0.651		0.218	0.516		-0.414	0.382		-0.289	0.378		0.003	0.780	
Illness Self	0.161	0.437		0.233	0.280		0.349	0.255		0.092	0.681		0.007	0.242	
Job loss	0.246	0.354		0.258	0.306		0.362	0.285		0.668	0.010		0.014	0.049	
Financial Problems	-0.136	0.667		0.289	0.332		0.788	0.057		**1.391**	**7.60E-05**		0.023	0.008	
End of Relationship	0.099	0.736		-0.120	0.738		-0.069	0.874		0.485	0.131		0.004	0.681	

Table 6.4. Continued

Life Events Considered Separately															
Life events	**B**	**p**	**R^2**	**B**	**p**	**R^2**	**B**	**p**	**R^2**	**B**	**p**	**R^2**	**B**	**p**	**R^2**
Accident	0.303	0.184	0.074	0.313	0.137	0.035	0.497	0.097	0.044	0.349	0.073	0.067	0.007	0.194	0.130
Violent Crime	0.175	0.695	0.073	0.667	0.068	0.035	0.002	0.997	0.043	0.254	0.482	0.066	-0.017	0.089	0.130
Sexual Crime	-0.491	0.142	0.074	-0.455	0.132	0.034	-0.511	0.316	0.043	**1.133**	**0.002**	**0.074**	0.024	0.012	0.134
Theft	-0.127	0.506	0.073	0.111	0.562	0.034	-0.097	0.723	0.043	-0.193	0.282	0.066	-0.012	0.012	0.131
Death of Partner	0.184	0.717	0.073	0.680	0.228	0.034	0.833	0.322	0.044	0.739	0.321	0.067	0.020	0.205	0.131
Death of Child	-0.530	0.533	0.073	1.068	0.146	0.033	0.627	0.582	0.043	0.712	0.453	0.066	0.004	0.822	0.129
Illness of Partner	-0.139	0.680	0.073	-0.384	0.268	0.034	-0.124	0.788	0.043	0.288	0.380	0.066	0.009	0.318	0.129
Illness of Child	0.186	0.594	0.073	0.284	0.395	0.034	-0.232	0.616	0.042	-0.031	0.926	0.065	0.007	0.419	0.130
Illness Self	0.181	0.397	0.073	0.257	0.228	0.034	0.382	0.211	0.044	0.240	0.278	0.067	0.010	0.102	0.132
Job loss	0.222	0.401	0.073	0.267	0.289	0.034	0.420	0.204	0.044	**0.867**	**0.001**	**0.074**	0.018	0.010	0.135
Financial Problems	-0.079	0.793	0.073	0.408	0.167	0.034	0.856	0.036	0.046	**1.650**	**2.90E-06**	**0.087**	**0.026**	**0.002**	**0.138**
End of Relationship	0.093	0.736	0.073	0.083	0.812	0.033	0.099	0.809	0.043	0.750	0.016	0.068	0.006	0.430	0.129

Note: Bold coefficients are significant (p<.002). B = unstandardized regression coefficient, R^2 = The proportion of variance in epigenetic age acceleration explained by the model

Table 6.5. GEE Analyses Investigating the Associations Between Epigenetic Aging and All Negative Life Events Estimated both *Simultaneously* and *Separately*, adjusted for Age, Sex, BMI, Smoking, and Technical Covariates.

	Hannum			IEAA			PhenoAge			GrimAge			DunedinPACE		
Life events	**B**	**p**	**R^2**	**B**	**p**	**R^2**	**B**	**p**	**R^2**	**B**	**p**	**R^2**	**B**	**p**	**R^2**
Any Life event	0.036	0.611	0.073	0.123	0.076	0.039	0.106	0.230	0.164	**0.285**	**3.19E-05**	**0.145**	0.004	0.010	0.264
Life Events Considered Simultaneously															
Life events	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**
Accident	0.285	0.199		0.244	0.236		0.245	0.405		0.130	0.412		-6.16E-04	0.900	
Violent Crime	0.220	0.635		0.606	0.094		0.055	0.924		-0.151	0.631		-0.021	0.022	
Sexual Crime	-0.585	0.092		-0.598	0.047		-0.771	0.082		0.309	0.271		0.009	0.272	
Theft	-0.134	0.497		0.076	0.697		-0.052	0.843		-0.269	0.072		-0.009	0.041	
Death of Partner	0.104	0.847		0.449	0.433		0.935	0.286		0.927	0.087		0.024	0.081	
Death of Child	-0.547	0.533		1.225	0.099		0.695	0.519		0.902	0.185		0.006	0.683	
Illness of Partner	-0.180	0.586	0.082	-0.572	0.105	0.048	-0.212	0.632	0.178	0.112	0.645	0.427	0.004	0.601	0.378
Illness of Child	0.143	0.679		0.181	0.593		-0.346	0.446		-0.395	0.129		3.82E-04	0.962	
Illness Self	0.141	0.496		0.199	0.355		0.419	0.135		0.385	0.026		0.012	0.015	
Job loss	0.267	0.312		0.238	0.341		0.215	0.500		0.328	0.093		0.009	0.112	
Financial Problems	-0.149	0.639		0.335	0.255		0.489	0.206		**0.875**	**0.001**		0.013	0.085	
End of Relationship	0.128	0.667		-0.042	0.907		-0.242	0.558		0.054	0.839		-0.003	0.686	

Table 6.5. Continued

Life Events Considered Separately															
Life events	**B**	**p**	**R^2**	**B**	**p**	**R^2**	**B**	**p**	**R^2**	**B**	**p**	**R^2**	**B**	**p**	**R^2**
Accident	0.292	0.202	0.079	0.308	0.140	0.041	0.329	0.259	0.173	0.280	0.075	0.413	0.002	0.609	0.365
Violent Crime	0.143	0.746	0.078	0.616	0.081	0.042	0.001	0.998	0.172	-0.082	0.787	0.412	-0.021	0.020	0.367
Sexual Crime	-0.521	0.123	0.079	-0.500	0.096	0.041	-0.669	0.127	0.173	0.442	0.118	0.413	0.010	0.212	0.366
Theft	-0.116	0.544	0.078	0.135	0.484	0.040	-0.012	0.963	0.172	-0.211	0.166	0.412	-0.010	0.029	0.366
Death of Partner	0.176	0.730	0.078	0.581	0.312	0.040	0.847	0.314	0.173	0.823	0.120	0.414	0.023	0.104	0.367
Death of Child	-0.533	0.528	0.078	1.112	0.130	0.040	0.724	0.496	0.172	1.143	0.096	0.413	0.010	0.509	0.365
Illness of Partner	-0.155	0.648	0.078	-0.420	0.224	0.041	-0.147	0.736	0.172	0.224	0.359	0.412	0.006	0.394	0.365
Illness of Child	0.169	0.632	0.078	0.231	0.491	0.041	-0.200	0.655	0.172	-0.179	0.503	0.412	0.005	0.566	0.365
Illness Self	0.157	0.463	0.078	0.222	0.297	0.041	0.405	0.147	0.173	0.451	0.008	0.415	0.013	0.009	0.368
Job loss	0.242	0.356	0.078	0.253	0.311	0.040	0.233	0.458	0.173	0.440	0.025	0.414	0.011	0.049	0.367
Financial Problems	-0.094	0.756	0.078	0.449	0.123	0.041	0.523	0.168	0.173	**1.002**	**2.32E-04**	**0.419**	0.014	0.053	0.367
End of Relationship	0.118	0.670	0.078	0.156	0.653	0.040	-0.100	0.796	0.172	0.249	0.338	0.412	-0.001	0.881	0.365

Note: Bold coefficients are significant (p<.002). B = unstandardized regression coefficient, R^2 = The proportion of variance in epigenetic age acceleration explained by the model

Discussion

Our study examined the impact of a broad spectrum of negative life events on epigenetic aging by analyzing five epigenetic biomarkers. This approach allowed us to perform both between-individual and within-twin pair comparisons, providing a nuanced view of how negative life events may affect the aging process. The results of our first analyses showed that the total number of experienced life events is associated with an acceleration of biological aging for the GrimAge biomarker. Further analysis refined these results by separately evaluating the influence of distinct life events. Initially, by estimating associations for all life events simultaneously in a single model, financial problems showed a clear age acceleration for the GrimAge biomarker. To isolate the effects of specific life events, we then compared respondents who experienced each life event against a control group that experienced no life events. This separate analysis highlighted several results: a pronounced effect of financial problems and of sexual crimes of approximately 1.1 years of age acceleration for the GrimAge biomarker. Job loss was associated with a 0.87 years increase. The DunedinPACE biomarker paralleled these findings, showing an increased pace of aging of roughly 10 days per chronological year for individuals who encountered sexual crimes and financial problems. These results show that not only the quantity but also the nature of life events are associated with epigenetic aging. Our findings resonate with and extend previous research that reported links between epigenetic biomarkers and childhood adversities, socioeconomic challenges, and PTSD (Joshi et al., 2023; Katrinli et al., 2023; Raffington et al., 2021; Yang et al., 2021). results extend these associations to a wider array of life events, with the most profound impacts observed in the context of financial strain and sexual crimes.

Diving deeper into our results, we incorporated additional covariates, specifically BMI, smoking habits, and white blood cell counts, to examine their influence on our previously observed associations. The incorporation of BMI, smoking habits, and white blood cell counts significantly modified the associations between life events and epigenetic aging. Notably, in the second model, which additionally accounted for BMI,

smoking and white blood cell count, several associations identified in the basic model lost their statistical significance, and the effect sizes were generally reduced. This shift underscores the potential confounding effects of these covariates, suggesting that the observed acceleration in biological aging, as measured by biomarkers like GrimAge and DunedinPACE, might be more intricately linked to broader lifestyle factors and physiological changes rather than directly attributable to life events themselves. The loss of significance of our findings post-adjustment show a complex interplay between life events, lifestyle choices, and biological factors and raises the possibility that lifestyle factors such as smoking or variations in BMI, potentially altered in response to life stressors, could be primary drivers of epigenetic changes. Similarly, fluctuations in white blood cell counts, might mediate the relationship between life events and biological aging. This complexity necessitates a cautious interpretation of the direct impact of life events on epigenetic aging. The sensitivity analyses, which included additional adjustments for EA alongside lifestyle factors and white blood cell counts, reaffirmed the associations of the GrimAge biomarker, with both the total number of life events experienced and financial problems. Notably, while financial problems were not statistically significant in the model that included all life events, the regression coefficient remained nearly unchanged and was just below the threshold for statistical significance. This shows that financial problems have a stable association with GrimAge acceleration, even when other life events and educational attainment are considered simultaneously. The lack of statistical significance in the comprehensive model may be due to the combined influence of multiple life events, which could dilute the specific effect of financial problems, or it may reflect decreased statistical power in a smaller sample. However, when financial problems were analyzed separately, they reached statistical significance, with the regression coefficient showing only a slight reduction compared to the models without EA. This indicates a robust impact of financial problems on biological aging, highlighting their importance as a predictor of GrimAge acceleration. Importantly, the fact that this association persists even after adjusting for educational attainment suggests that financial problems are associated with accelerated biological aging independent of socioeconomic status. This persistence

shows a potentially robust link between specific stressors and epigenetic aging, warranting further investigation. These observations are in line with previous research which found that that PTSD was associated with GrimAge acceleration (Katrinli et al., 2023; Yang et al., 2021).

Our study further delved into the age acceleration findings from the population analyses by conducting discordant MZ twin analyses. By examining MZ twin pairs with differing life event experiences, we controlled for shared genetic and environmental factors, providing a more unobstructed view of the relationship between life adversities and biological aging. In our sample of 411 MZ pairs, we found that 263 pairs were discordant and 148 concordant for the number of life events experienced. The high concordance in MZ pairs is consistent with genetic modeling of the life event data (Middeldorp et al., 2008) which show that genetic and common environmental factors play a substantial role in the individual differences in the experience of life events. This finding aligns with the notion that genetic predispositions may influence the likelihood of encountering or perceiving certain life events. However, the limited number of discordant MZ twin pairs regarding specific life events implies a lower statistical power. Consequently, we chose to focus our analysis on the total number of life events, rather than specific ones, as the variability within discordant pairs was insufficient to robustly assess the impact of specific life events. Intriguingly, when looking at the association between the total number of life events experienced and age acceleration in terms of GrimAge, the effect sizes of the population were reduced by more than half in the discordant twin analyses. This finding suggests that the observed acceleration at the population level in biological aging requires a more complex and nuanced explanation than that of a direct causal effect by life events. Rather than expressing a causal effect, the associations are likely confounded by shared family factors, genetic and/or environmental. These factors might predispose individuals to both experience certain life events and exhibit specific patterns of biological aging. The discordant twin model thus provides a more stringent test of the relationship between life events and biological aging. It is also possible that the impact of a life event experienced by one twin could affected the co-twin, particularly

in cases of more severe incidents like the loss of a child and sexual crimes. The shared environment and emotional bonds between twins mean that a traumatic event affecting one twin could also have psychological, behavioral, or even biological repercussions for the other. Alternatively, financial and emotional support from a twin may reduce the impact of a life event. These inter-twin influences might lead to an underestimation of the effects in the MZ twin model. To further unravel the complexities observed in this study, future research should enhance discordant twin pair analyses, potentially with larger sample sizes, to assess the persistence of associations when adjusting for genetic and environmental influences. This approach will be crucial in clarifying the extent to which genetic and shared environmental factors may confound the relationship between life events and epigenetic aging.

Despite the strengths of our study, it is not without its limitations. Firstly, in the discordant twin analyses, we could only look at the total number of life events and were unable to examine the specific life events, thereby limiting our capacity to draw conclusions regarding the possible genetic and shared environmental confounding between experiencing any particular life events and epigenetic aging.

Secondly, the subjective nature of how individuals perceive and report life events presents another challenge (Kessler & Wethington, 1991; Van de Mortel, 2008). For instance, the significance of an event like theft can vary greatly; one person may not consider the theft of a bicycle significant enough to report it, while another might. Although one might also argue that it is the subjective experience that matters rather than the event taking place, this subjectivity still poses a challenge in standardizing and comparing experiences across individuals. Furthermore, there is substantial variability in the severity of incidents within the same category. For instance, a home burglary is generally more severe than bicycle theft and severe assault is more impactful than a mere threat. This variation in severity, coupled with the subjective experience of respondents, makes it complex to categorize and assess the impact of life events. Future research, including longitudinal studies, and more additional information about event severity, and the support that people receive after having experienced a life event, could

help to unravel these complex relationships. Additionally, applying a Cholesky decomposition model to both life events and epigenetic biomarkers could offer valuable insights by distinguishing the unique and shared variance between these factors.

In conclusion, our study has shed light on the intricate interplay between life events and epigenetic aging, highlighting the profound impact of experiencing life events on the biological aging processes. While our analyses reveal that lifestyle factors and white blood cell counts can partly explain the association between experiencing negative life events and aging, our findings highlight the significant impact of financial difficulties and experiencing multiple life events on biological aging, even after accounting for these variables. Thus, policy initiatives aimed at reducing financial hardships among citizens could also have positive implications for their health. By focusing on lessening financial stress, these policies might contribute to mitigating the accelerated aging associated with such stressors. The discordant monozygotic twin analysis adds a layer of complexity to our understanding as they suggested that familial factors may confound the observed associations. This outcome highlights the need for caution in interpreting these relationships between experiencing negative life events and epigenetic aging and underscores the importance of further research in this area. This study not only reinforces the importance of considering a broad spectrum of life events in epigenetic aging research but also calls for more nuanced, longitudinal studies that can address the limitations we identified, such as the varying interpretations of life event severity and the need for larger sample sizes for rare events. This work reinforces the importance of considering both genetic and environmental factors in the study of epigenetics and aging.

Chapter 7.

Slachtofferschap en Biologische Veroudering

Abstract

Dit onderzoek richtte zich op de relatie tussen slachtofferschap van criminaliteit en biologische leeftijd. Bij 2,210 volwassen deelnemers uit het Nederlandse Tweelingenregister onderzochten we vijf epigenetische biomarkers: Hannum, Horvath, PhenoAge, GrimAge en DunedinPACE. Er was geen verband tussen vermogens- en geweldsmisdrijven en biologische veroudering. Recent slachtofferschap van zedencriminaliteit hield verband met een toename in biologische leeftijd op drie biomarkers. Op de DunedinPACE vonden we bij zedenslachtoffers een toename van de snelheid van veroudering van 60 dagen per jaar. Behalve deze, verdwenen de meeste verbanden na statistische correctie voor witte bloedcellen, BMI en rookstatus, wat suggereert dat levensstijl een rol speelt. Om te corrigeren voor genetische en omgevingsfactoren hebben we vervolgens de analyses herhaald bij eeneiige tweelingparen waarvan de één een delict heeft meegemaakt en de tweelingbroer of -zus niet. Hoewel, de gevonden verbanden in deze analyses niet meer significant waren, waren de effectgroottes vergelijkbaar. Dit suggereert dat de versnelde biologische veroudering van zedenslachtoffers mogelijk een causaal effect is.

Ingediend als: Gonggrijp, B. M. A., van de Weijer, S. G. A., Bijleveld, C. C. J. H., Boomsma, D. I., & van Dongen, J. (ingediend voor publicatie). Slachtofferschap en Biologische Veroudering

English Summary

This study focused on the relationship between crime victimization and biological age. We examined five epigenetic biomarkers — Hannum, Horvath, PhenoAge, GrimAge, and DunedinPACE — among 2,210 adult participants from the Netherlands Twin Register. There was no association between property or violent crime and biological aging. However, recent victimization of sexual crime was linked to an increase in biological age on three biomarkers. For sexual crime victims, we found an acceleration in aging speed of 60 days per year on the DunedinPACE. Most associations, except for this one, disappeared after statistical adjustments for white blood cells, BMI, and smoking status, suggesting that lifestyle factors play a role. To account for genetic and environmental factors, we repeated the analyses in identical twin pairs, where one twin had experienced a crime and the other had not. Although the associations were no longer significant in these analyses, the effect sizes were similar, suggesting that the accelerated biological aging of sexual crime victims may be a causal effect.

Submitted as: Gonggrijp, B. M. A., van de Weijer, S. G. A., Bijleveld, C. C. J. H., Boomsma, D. I., & van Dongen, J. (submitted for publication). Slachtofferschap en Biologische Veroudering

Slachtofferschap en Biologische Veroudering

Er is een verband tussen slachtofferschap en diverse geestelijke en lichamelijke gezondheidsproblemen, zoals hart- en vaatziekten, prikkelbare darm syndroom, frequente hoofdpijn en chronische pijn (Ann Priester et al., 2016; Bindler, Ketel, & Hjalmarsson, 2020). Ook is er een verband tussen slachtofferschap en vroegtijdige sterfte (Brown et al., 2009; Pridemore & Berg, 2017; Wang et al., 2023). De relatie tussen slachtofferschap en gezondheidsproblemen is echter complex. Naast de directe impact van trauma op lichaam en geest, kunnen indirecte mechanismen een rol spelen die deze effecten over de lange termijn versterken, in stand houden, of doen afnemen. Daarbij kunnen epigenetische veranderingen [3] een rol spelen. Epigenetische veranderingen kunnen tot stand komen door externe factoren zoals stress, voeding, en blootstelling aan trauma (Jiang et al., 2019; Nöthling et al., 2020), en kunnen gevolgen hebben voor de gezondheid op langere termijn (Stankiewicz, Swiergiel, & Lisowski, 2013). In epidemiologische studies kan DNA-methylatie worden gemeten bij grote groepen deelnemers met array technologie (van Dongen et al., 2022). De array gegevens, 400.000 tot 800.000 datapunten per persoon, kunnen worden samengevat in scores waarmee een inschatting gemaakt kan worden van iemands 'biologische' leeftijd (Raffington & Belsky, 2022). Als iemands biologische leeftijd hoger is dan de chronologische leeftijd, spreken we van 'epigenetische leeftijdsversnelling'. Die versnelling hangt samen met een verhoogd risico op sterfte (Marioni, Shah, McRae, Chen, et al., 2015) en met nadelige gezondheidsuitkomsten, zoals cognitieve stoornissen en slechte fysieke en cognitieve fitheid (Levine et al., 2015; Marioni, Shah, McRae, Chen, et al., 2015).

De eerste generatie biologische markers voor epigenetische leeftijdsversnelling zijn de Hannum- en Horvath biomarkers (Hannum et al., 2013; Horvath, 2013), die weliswaar goed de chronologische leeftijd kunnen voorspellen, maar minder goed bleken in het voorspellen van aan leeftijd gerelateerde aandoeningen, waaronder ziekten en afnames

[3] Epigenetische veranderingen kunnen ontstaan doordat een methylgroep - een kleine chemische structuur die bestaat uit één koolstofatoom gebonden aan drie waterstofatomen (CH_3) - zich aan het DNA hecht. Hierbij verandert de DNA-sequentie zelf niet, maar wel de genexpressie, het tot uiting komen van een gen.

in fysiologische en functionele capaciteiten (Bell et al., 2019; Hannum et al., 2013; Horvath, 2013). Een volgende generatie epigenetische biomarkers, waaronder PhenoAge en GrimAge, werd ontwikkeld om de resterende levensduur en dus sterfterisico van een individu te voorspellen . GrimAge (naam verwijst de "Grim Reaper," oftewel de Dood) neemt factoren zoals leeftijd, geslacht en rookgedrag mee. PhenoAge is afgeleid van fysiologische indicatoren (bloeddruk, cholesterolwaarden en ontstekingsindicatoren), die gebaseerd zijn op DNA-methylatiegegevens. Zowel GrimAge als PhenoAge zijn nauwkeuriger in het voorspellen van morbiditeit en mortaliteit dan de eerste generatie biomarkers (Levine et al., 2015; Lu et al., 2019). Recent is DunedinPACE ontwikkeld, een derde generatie epigenetische biomarker die snelheid van veroudering schat. Terwijl de Hannum, Horvath, PhenoAge en GrimAge biomarkers worden geïnterpreteerd als biologische leeftijd in jaren, geven de waarden van DunedinPACE het verouderingstempo in één chronologisch jaar aan (Belsky et al., 2022). De epigenetische biomarkers zijn onderling gecorreleerd. [4]

Een aanzienlijk aantal studies heeft gekeken naar de relatie tussen nadelige ervaringen in de kindertijd en epigenetische veroudering, met afwijkende bevindingen per biomarker. Marini et al. (2020) en Tang et al. (2020) onderzochten de relatie van stressvolle levensgebeurtenissen in de kindertijd met epigenetische versnelling volgens de Horvath en Hannum biomarkers, met data uit een Amerikaans geboorte cohort (N=974). Zij vonden dat blootstelling aan negatieve levensgebeurtenissen en aan emotioneel en fysiek misbruik geassocieerd was met epigenetische veroudering volgens de Horvath biomarker onder meisjes en met veroudering volgens de Hannum biomarker onder zowel jongens als meisjes. Ook Jovanovic et al. (2017) onderzochten de relatie tussen blootstelling aan geweld in de kindertijd en epigenetische veroudering, gemeten met de Horvath biomarker, onder 101 Afro-Amerikaanse kinderen van 6-13 jaar.

[4] De Hannum-, Horvath- en PhenoAge-biomarkers zijn matig tot sterk gecorreleerd, variërend van r= 0,33 tot r= 0,84 (Lu et al., 2019; McCrory et al., 2021) terwijl GrimAge en DunedinPACE matig zijn gecorreleerd (r= 0,61; Föhr et al., 2024).

Kinderen die biologisch ouder waren dan hun chronologische leeftijd hadden twee keer zoveel blootstelling aan geweld ervaren.

Recenter onderzoek includeerde ook de tweede generatie biomarkers. Joshi et al. (2023) lieten onder 1445 Canadese individuen van 45-85 jaar zien dat blootstelling aan ouderlijke scheiding of emotioneel misbruik in de kindertijd samenhangt met epigenetische leeftijdsversnelling op latere leeftijd volgens de GrimAge, maar niet de PhenoAge biomarker. McCrory et al. (2022) onderzochten negatieve gebeurtenissen tijdens de kindertijd bij 490 Ierse volwassenen tussen de 50-87 jaar, en vonden een verband tussen armoede in de kindertijd en versnelde biologische veroudering volgens de Grimage en DunedinPACE biomarkers, maar niet voor overige gebeurtenissen (dood van een ouder, drugs- of alcoholmisbruik van ouders, fysiek of seksueel misbruik) tijdens de kindertijd. Belsky et al. (2022) kwamen tot soortgelijke conclusies onder deelnemers uit de E-Risk Longitudinale Studie (N= 1.658), en vonden daarnaast een verband tussen polyvictimisatie (het herhaaldelijk slachtoffer zijn van verschillende soorten misbruik en geweld) en versnelde veroudering. Kim et al. (2023) volgden 895 jongvolwassenen vanaf 15 tot 20 jaar, en vonden versnelde biologische veroudering zoals gemeten met de PhenoAge, GrimAge en DunedinPACE markers bij meer negatieve jeugdervaringen. Deze effecten hielden stand tot in de volwassenheid, ook na correctie voor demografische en sociaaleconomische variabelen. Een vergelijkbare studie van Suglia et al. (2022) keek naar stressvolle levenservaringen (waaronder slachtofferschap) vanaf de kindertijd tot de volwassenheid, gemeten tijdens geboorte, 9, 15 en 50 jaar, en biologische veroudering in de volwassenheid (50 jaar). Stress tijdens de kindertijd en in het volwassen leven voorspelden onafhankelijk versnelde biologische veroudering, zoals gemeten door GrimAge, en een hogere verouderingssnelheid, zoals gemeten door de DunedinPACE biomarker.

Onderzoek naar epigenetische effecten van slachtofferschap in de volwassenheid is tot nu toe voornamelijk beperkt gebleven tot partner- en oorlogsgeweld. Bourassa et al. (2020) onderzochten partnergeweld onder de deelnemers van de Dunedin Studie (N= 974) en vonden dat partnergeweld gecorreleerd was met een toename in

verouderingstempo in de DunedinPACE biomarker. Katrinli et al. (2023) onderzochten 140 mannelijke veteranen blootgesteld aan oorlogsgeweld, waaronder 112 met posttraumatische stressstoornis (PTSS), en 59 mannelijke burgers niet blootgesteld aan trauma. Zij vonden biologische veroudering volgens de GrimAge biomarker bij de deelnemers met PTSS, en geen verschil tussen de veteranen zonder PTSS en de controlegroep. Yang et al. (2021) vonden vergelijkbare verbanden tussen PTSS en verhoogde biologische veroudering op de GrimAge biomarker.

Samenvattend laten de eerder uitgevoerde onderzoeken zien dat blootstelling aan stressvolle en traumatische ervaringen, zowel in de kindertijd als in de volwassenheid, geassocieerd is met versnelde biologische veroudering. Deze versnelling varieert echter afhankelijk van de specifieke biomarker en het type negatieve ervaring. Sommige trauma's, met name partnergeweld, oorlogsgeweld en polyvictimisatie, hebben een grotere invloed op de epigenetische veroudering dan andere stressoren.

De Huidige Studie

In dit onderzoek richten wij ons op de relatie tussen slachtofferschap en epigenetische leeftijd bij volwassenen uit de Nederlandse bevolking. We gebruiken een grote, uit de algehele populatie afkomstige, steekproef van families uit het Nederlandse Tweelingenregister (NTR; N= 2,110 personen). We richten ons op slachtofferschap van geweldsmisdrijven, zedenmisdrijven en diefstal, en de relatie met de vijf meest onderzochte epigenetische biomarkers: Hannum, Horvath, PhenoAge, GrimAge en DunedinPACE. We onderzoeken eerst het verband tussen deze soorten slachtofferschap en epigenetische leeftijdsversnelling onder alle deelnemers van het NTR. Hierbij wordt ook gekeken of eventuele verbanden afhankelijk zijn van het feit dat het slachtofferschap recent is of niet. Wat deze studie uniek maakt, is de herhaling van deze analyses onder een groep van eeneiige tweelingparen, waarbij de ene tweeling wel en de co-tweeling niet slachtoffer is geweest. Omdat eeneiige tweelingen een identieke genetische aanleg hebben en veel omgevingsfactoren ook hetzelfde zijn, controleren we zo voor vertekening door gedeelde onderliggende factoren, die zowel de blootstelling aan een misdrijf als de uitkomst beïnvloeden (Gesell, 1942; Gonggrijp et al., 2023).

Daarnaast onderscheidt deze studie zich door diverse soorten slachtofferschap te onderzoeken, waar eerder onderzoek zich met name richtte op PTSS of specifieke trauma's zoals oorlogsgeweld.

Methode

Steekproef

De data zijn verzameld bij tweelingen, hun ouders, broers en zussen, partners en kinderen die deelnemen aan studies onder volwassenen van het Nederlandse Tweelingenregister (NTR: https://tweelingenregister.vu.nl/). Deelnemers vullen elke twee tot drie jaar vragenlijsten in over gezondheid en levensstijl (zie over de gegevensverzameling bijvoorbeeld Ligthart et al. (2019); Middeldorp et al. (2008)). Voor dit artikel analyseerden we DNA-methylatie gemeten in bloed verzameld in de NTR-Biobank-studie, uitgevoerd in 2004-2008 en 2010-2011 (Sirota et al., 2015; Van Asselt et al., 2023; Van Dongen et al., 2016). Slachtofferschap werd bevraagd in 2009, 2004, 2002 en 2000. Niet-slachtoffers werden geselecteerd als controle personen als zij in de meest recente (2009) survey hadden gerapporteerd dat zij nooit slachtoffer waren geworden. De data van slachtoffers werden geanalyseerd als hun DNA was verzameld *na* het slachtofferschap.

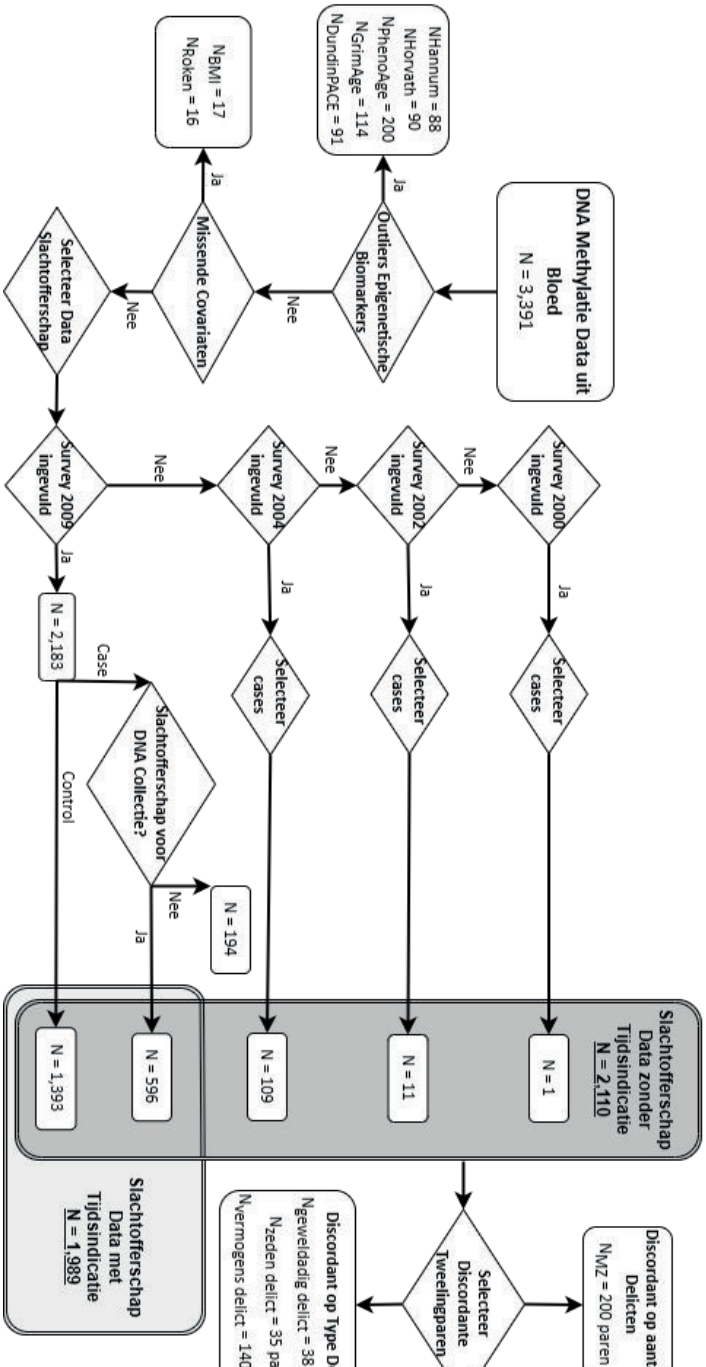
Variabelen

Slachtofferschap

In de 2009, 2004, 2002 en 2000 NTR-vragenlijst werd gebruik gemaakt van de Schokverwerkings Inventarisatie Lijst (Middeldorp et al., 2008; van der Ploeg et al., 2004) die vraagt: “Welke gebeurtenissen zijn u in uw leven overkomen?”. Hierbij werden deelnemers ook gevraagd naar slachtofferschap van vermogensmisdrijven (diefstal, inbraak of vernieling), geweldsmisdrijven (overval, lichamelijk geweld) en zedenmisdrijven (verkrachting, aanranding), met de antwoordcategorieën "nooit meegemaakt", "minder dan 1 jaar geleden", "1-5 jaar geleden" en "meer dan 5 jaar geleden meegemaakt".

Voor slachtoffers werden in eerste instantie de gegevens uit de 2009-survey gebruikt, indien het slachtofferschap *vóór* de bloedafname had plaatsgevonden. Voor slachtoffers keken we naar de tijdsperioden "minder dan 1 jaar geleden", "1-5 jaar geleden" en "meer dan 5 jaar geleden" zoals gerapporteerd in de 2009-survey. Omdat de prevalentie van "minder dan 1 jaar geleden", "1-5 jaar geleden" relatief klein was, zie Tabel 7.1, werden deze antwoord categorieën samengevoegd tot “0 – 5 jaar geleden”. Daarnaast creëerden we een aparte binaire variabele voor het ooit hebben meegemaakt van slachtofferschap uit de gegevens van de vragenlijsten van zowel 2009, als 2004, 2002 en 2000. Zie figuur 7.1 voor een overzicht van de stappen in de dataselectie. Ook is er een somscore gecreëerd van de verschillende typen delicten, om zo te kunnen kijken naar polyvictimisatie.

De tijd tussen de afname van de 2009-vragenlijst en de afname van het DNA varieerde onder deelnemers, de gemiddelde tijd tussen de vragenlijst en DNA-afname was 1.98 jaar. De rapportage van een gebeurtenis minder dan vijf jaar geleden weerspiegelt dus niet exact het effect van een gebeurtenis minder dan vijf jaar geleden. Om te bepalen of de tijd tussen het invullen van de vragenlijst en de DNA-afname varieerde tussen de verschillende slachtoffergroepen, werden Kruskal-Wallis-testen uitgevoerd. Er werden geen significante verschillen gevonden.



Figuur 7.1. Stroomschema voor de selectie van DNA-methylatiegegevens en slachtofferschap. N.B. Slachtofferschap data met tijdsindicatie: gegevens uit de 2009-survey waarbij de tijdsperiode van slachtofferschap is gerapporteerd ("minder dan 1 jaar geleden", "1-5 jaar geleden", "meer dan 5 jaar geleden"), N= 1,989. Slachtofferschap data zonder specifieke tijdsindicatie: gebaseerd op zowel de 2009 survey als eerdere survey's (2000, 2002, 2004). Totale N (2,110) bevat slachtoffers en niet-slachtoffers.

DNA-methylatie biomarkers van biologische veroudering.

De metingen van DNA methylatie zijn elders beschreven (Gonggrijp, van de Weijer, Bijleveld, Boomsma, & van Dongen, 2024; Van Asselt et al., 2023; Van Dongen et al., 2016). In eerder onderzoek keken wij naar het meemaken van negatieve levenservaringen en epigenetische leeftijdsversnelling onder deelnemers van het NTR met Illumina 450k array data (Gonggrijp et al., 2024). Het huidige onderzoek is gebaseerd op een gedeeltelijk overlappend steekproef. Het huidige onderzoek verschilt ten op zichten van het vorige op de volgende punten: 1) een grotere steekproefgrootte door toevoeging van nieuwe Illumina EPIC array data van extra deelnemers, zoals beschreven in de aanvullende methoden (Supplementary Methods S7.1) 2) deze grotere steekproefgrootte maakte een uitsplitsing van de gerapporteerde delicten korter dan 5 jaar geleden vs. langer dan 5 jaar geleden mogelijk, 3) verbeterde schatting van epigenetische biomarkers door herberekening op basis van de nieuwste software (in het vorige onderzoek analyseerden wij de oudere versies van DNAmPhenoAge en GrimAge en in het huidige onderzoek analyseerden wij “PCPhenoAge” en “PCGrimAge”, Higgins-Chen et al., 2022). Op basis van de DNA methylatie profielen zijn vijf epigenetische biomarkers van veroudering berekend met het R pakket “dnaMethyAge”. Voor elk van deze epigenetische biomarkers werden outliers beoordeeld en datapunten van de deelnemers werden verwijderd wanneer ze 3 keer boven of onder het interkwartielbereik lagen (Horvath= 88, Hannum= 90, PhenoAge= 200, GrimAge= 114 en DundinPACE= 91). De leeftijdsversnellingswaarden van de Hannum, Horvath, PhenoAge en GrimAge biomarkers zijn op dezelfde schaal. Een waarde van 0 betekent dat iemands biologische leeftijd gelijk is aan zijn of haar chronologische leeftijd, terwijl waarden groter dan 0 geïnterpreteerd worden als versnelde veroudering en waarden kleiner dan 0 als vertraagde veroudering. De DunedinPACE schat geen biologische leeftijd (in jaren) maar het tempo van veroudering, dat aangeeft hoe snel iemand biologisch veroudert ten opzichte van zijn of haar chronologische leeftijd. Waarden liggen rondom de 1 (minimum: 0), waarbij een waarde van 1 overeenkomt met een normaal verouderingstempo van 1 biologisch jaar per chronologisch jaar. Waarden groter dan 1 duiden op een versneld verouderingstempo, en waarden kleiner dan 1 op een vertraagd

tempo. Bijvoorbeeld, een waarde van 1.4 betekent dat iemand in één chronologisch jaar, 1.4 jaar biologisch ouder wordt.

Covariaten

DNA-methylatie wordt gemeten met DNA-methylatie microarrays, die gevoelig kunnen zijn voor technische variatie. Om te corrigeren voor eventuele systematische fouten of variabiliteit die niet gerelateerd is aan biologische variatie zijn een aantal zogeheten technische covariaten, te weten array rij en bisulfiet-plaat [5] toegevoegd.

Daarnaast werden geslacht en chronologische leeftijd (Krieger et al., 2023) op het moment van bloedafname opgenomen als covariaten om te corrigeren voor mogelijke effecten van sekse en leeftijd, evenals leefstijl-gerelateerde factoren zoals Body Mass Index (BMI) en rookstatus. BMI werd berekend op basis van het gerapporteerde gewicht en de lengte (kg/m^2) op het moment van bloedafname en fungeert als een proxy voor metabole gezondheid. Rookstatus werd gecategoriseerd als niet-roker (gecodeerd als 0), ex-roker (gecodeerd als 1) en huidige roker (gecodeerd als 2), eveneens bepaald op het moment van bloedafname en dient als een indicator van leefstijl.

Epigenetische leeftijdsversnelling, gemeten in een bloedmonster, kan samenhangen met de verhouding van de verschillende soorten witte bloedcellen, aangezien elk celtype unieke epigenetische patronen vertoont. Om ervoor te zorgen dat de resultaten niet worden vertekend door variaties in celtypen, zijn de proporties witte bloedcellen opgenomen in de analyses als covariaten. [6]

[5] De array-rij geeft de positie van de monsters op de microarray aan, en de bisulfiet-plaat verwijst naar de laboratoriumplaat gebruikt bij de DNA-bisulfietbehandeling , een cruciale stap voor het meten van methylatie.

[6] De proporties witte bloedcellen die aanwezig zijn in een bloedmonster werden geschat op basis van het DNA methylatieprofiel met het R pakket IDOL (identifying optimal DNA methylation libraries (Aryee et al., 2014). In de analyses werd gecorrigeerd voor: neutrofielen, CD4 T-cellen, CD8 T-cellen, monocyten, B-cellen. Om multi-collineariteit te voorkomen werd er niet gecorrigeerd voor Natural Killer cellen (NK).

Statistische analyses

Analyse hele steekproef

Als eerste werd het verband onderzocht tussen slachtofferschap en epigenetische leeftijdsversnelling voor de hele steekproef. Om rekening te houden met clustering binnen families zijn generalized estimation equations (GEE) modellen gebruikt, met behulp van het R-pakket GEE, met een Gaussische linkfunctie, 100 iteraties, en de 'exchangeable' optie om rekening te houden met correlatiestructuren binnen families. Epigenetische leeftijdsversnelling was de afhankelijke variabele, met de drie vormen van slachtofferschap als onafhankelijke variabelen in één model, onderverdeeld per tijdsperiode: geen slachtofferschap, minder dan 5 jaar, of meer dan 5 jaar geleden meegemaakt. Er werden twee modellen geschat. In het eerste model werd gecorrigeerd voor chronologische leeftijd (Krieger et al., 2023), geslacht en technische covariaten. We weten dat nadelige lange-termijn effecten van slachtofferschap op epigenetische leeftijdsversnelling mogelijk vertekend worden door een ongezondere leefstijl en/of door een veranderd witte bloedcelprofiel, daarom werd er in een tweede model additioneel gecorrigeerd voor roken, BMI en proportie witte bloedcellen (omdat de Hannum biomarker de geschatte samenstelling van witte bloedcellen al meeneemt in de berekening van de biologische leeftijd, is bij analyses met de Hannum biomarker de proportie witte bloedcellen niet meegenomen als covariaat).

Analyse discordante tweelingen

Het verband tussen slachtofferschap en epigenetische veroudering werd nader onderzocht door te kijken naar discordante eeneiige (i.e., monozygote - MZ) tweelingparen, waar de ene tweeling slachtoffer was geweest van een type delict en de ander niet. Om te kijken naar het effect van polyvictimisatie werd een tweeling als discordant beschouwd wanneer ze niet hetzelfde aantal delicten hadden gerapporteerd. Dit design corrigeert voor alle genetische en gedeelde omgeving confounding, en voor effecten die direct samenhangen met leeftijd en geslacht. Als het verband tussen slachtofferschap en epigenetische leeftijdsversnelling causaal is, verwachten we dat zowel de analyses in de hele steekproef als in de discordante MZ-tweelingen een verband laten zien tussen slachtofferschap en epigenetische leeftijdsversnelling. Echter,

wanneer er een associatie is in de hele steekproef, maar niet of zwakker bij de discordante tweeling paren, betekent dit dat familiale factoren (genetisch en/of gedeelde omgeving) de relatie tussen slachtofferschap en epigenetische leeftijdsversnelling mede bepalen (Gonggrijp et al., 2023).

Gegeven de kleinere aantallen discordante tweelingparen is er in deze analyses geen uitsplitsing gemaakt naar het moment van slachtofferschap (< 5 jaar geleden of > 5 jaar geleden) maar werden slechts slachtoffers en niet-slachtoffers onderscheiden. Voor deze analyses werden dezelfde modellen aangehouden als in de analyses voor de gehele steekproef, behalve dat leeftijd en sekse niet als covariaten opgenomen werden omdat MZ-tweelingen dezelfde leeftijd en sekse hebben. De discordante tweeling-analyses werden uitgevoerd met fixed-effects regressie in R.

Correctie voor meervoudig testen

Correctie voor meervoudig testen werd gedaan met een Bonferroni-correctie voor het aantal onafhankelijke testen (α= 0.05/N onafhankelijke dimensies. Om het aantal onafhankelijke dimensies te bepalen, werd Matrix Spectrale Decompositie (Nyholt, 2004) gebruikt in R. Er werden twee onafhankelijke dimensies geïdentificeerd gerelateerd aan slachtofferschap en vier met betrekking tot de epigenetische biomarkers. Dit resulteerde in 2*4 = 8 onafhankelijke dimensies en een aangepaste α van 0.006. De betrouwbaarheidsintervallen (in figuren) werden aangepast naar dit significantieniveau.

Resultaten

Beschrijvende statistieken

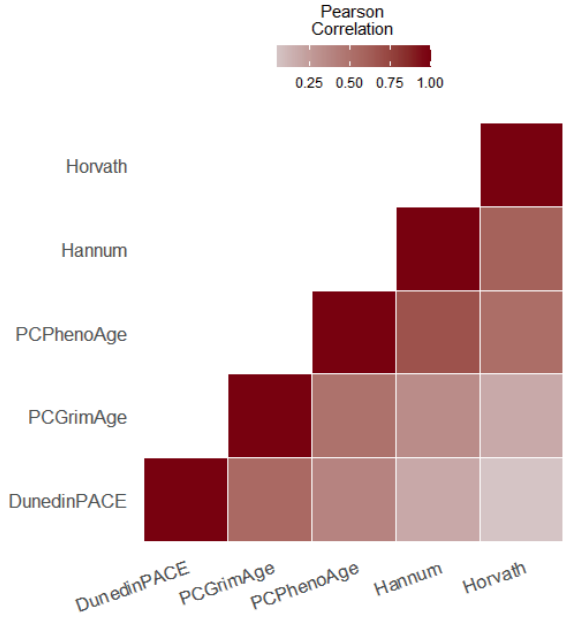
De prevalentie van elk type slachtofferschap is weergegeven in tabel 7.1. Het meest voorkomende slachtofferschap is van een vermogensmisdrijf, dat het vaakst werd gerapporteerd als langer dan 5 jaar geleden (18.84%). Het recent meemaken van een zedenmisdrijf heeft de laagste prevalentie (0.43%). In de gehele steekproef had 0.66 % alle drie de type delicten meegemaakt. Tabel 7.2 geeft de beschrijvende statistieken voor de epigenetische biomarkers, de witte bloedcellen, BMI en rookstatus. De

gemiddelde leeftijd ten tijde van DNA-afname was 37.23 jaar (SD= 12.88) en het merendeel van de deelnemers was vrouw (70.46%). De correlaties tussen de epigenetische biomarkers zijn weergegeven in de heatmap in Figuur 7.2, waaruit blijkt dat deze biomarkers onderling zwak tot matig gecorreleerd zijn.

Tabel 7.1. Overzicht prevalentie van elk type misdrijf.

	Zedenmisdrijf		**Geweldsmisdrijf**		**Vermogensmisdrijf**	
	N	**%**	**N**	**%**	**N**	**%**
Niet meegemaakt	1848	92.91%	1881	94.57%	1541	78.26%
0–5 jaar geleden meegemaakt*	7	0.35%	17	0.85%	77	3.91%
5+ jaar geleden meegemaakt*	134	6.74%	91	4.58%	351	17.83%
	N	**%**	**N**	**%**	**N**	**%**
Niet meegemaakt	1949	92.37%	1972	93.46%	1554	73.65%
Ooit meegemaakt	161	7.63%	138	6.54%	556	26.35%

	Aantal meegemaakte delicten			
Polyvictimisatie	**0**	**1**	**2**	**3**
N	1393	593	110	14
%	66.02%	28.10%	5.21%	0.66%



Figuur 7.2. Heatmap van de correlaties tussen de epigenetische biomarkers. De kleuren in de heatmap tonen de sterkte van positieve correlaties tussen de epigenetische biomarkers, waarbij donkere kleuren sterkere correlaties aangeven en lichtere kleuren zwakkere.

Tabel 7.2. Beschrijvende statistieken van de totale steekproef

Variabele	N	Min	Max	Gemiddelde	SD
Hannum	2060	-20.757	42.231	0.004	3.648
Horvath	2060	-25.472	31.833	0.059	2.876
PhenoAge	1982	-21.975	38.241	-0.115	4.623
GrimAge	2050	-8.327	13.985	-0.264	2.840
DunedinPACE	2047	0.590	1.358	0.933	0.105
Leeftijd*	2110	17	79	37.229	12.842
BMI	2110	14.600	48.900	24.227	3.936
Witte Bloedcellen					
B Cellen	2110	0.008	0.407	0.060	0.024
Monocyten	2110	0.024	0.226	0.085	0.023
CD4 T-Cellen	2110	-1.21E-19	0.452	0.178	0.061
CD8 T-Cellen	2110	-5.38E-19	0.481	0.123	0.049
Neutrofilen	2110	0.037	0.840	0.514	0.093
	N	**%**			
Biologisch geslacht (ref = vrouw)	1489	70.57%			
Roken					
Nooit gerookt	1228	58.20%			
Ex - roker	505	23.93%			
Huidige Roker	337	15.97%			

* leeftijd ten tijde van DNA afname. Alle biomarkers betreffen epigenetische leeftijdsversnelling.

Analyse gehele steekproef

De resultaten van de analyses in de gehele steekproef zijn weergegeven in Tabel 7.3, voor zowel het model gecorrigeerd voor chronologische leeftijd, geslacht en technische covariaten als het model waarbij additioneel gecorrigeerd is voor rookgedrag, BMI en witte bloedcellen. Het meemaken van vermogens- of geweldsmisdrijven hield geen verband met enige biomarker. In het eerste model was er een significant positief verband tussen meerdere biomarkers en het meemaken van een zedenmisdrijf, indien dit was gerapporteerd als recent meegemaakt (0 – 5 jaar geleden), voor de Hannum (B = 4.311, p = 1.47E-05), PhenoAge (B = 6.988, p = 6.06E-53), GrimAge (B = 3.714, p = 0.001) en DunedinPACE (B = 0.164, p = 9.00E-60) biomarkers. Recent slachtofferschap van zedenmisdrijven houdt dus verband met snellere epigenetische veroudering. Aangezien de Hannum, PhenoAge en GrimAge biomarkers worden uitgedrukt als het residu uit de regressie van de geschatte biologische leeftijd op de chronologische leeftijd, betekent

dit dat het recent meemaken van slachtofferschap zich vertaalt in een verhoogde biologische leeftijd van respectievelijk 4, 7 en 4 jaar volgens de respectievelijke biomarkers. De DunedinPACE biomarker is een maat voor het tempo van veroudering, zodat de coëfficiënt van 0.164 een toegenomen tempo van veroudering van 0.164, wat overeenkomt met respectievelijk 60 dagen, ofwel 8.5 weken, versnelling in 1 chronologisch jaar.

In het model, dat additioneel corrigeerde voor rookgedrag, BMI en de proportie witte bloedcellen was het verband tussen het meemaken van een recent zedenmisdrijf niet meer significant voor de GrimAge biomarker (B= 0.273, p= 0.709) en de PhenoAge biomarker (B= 2.244, p= 0.007). De regressiecoëfficiënten van deze gevonden verbanden in model 1, reduceerden sterk na de additionele correctie. Er bleef echter een significant verband tussen recente zedenmisdrijven en zowel de Hannum biomarker (B= 4.468, p= 2.18 E-06) als de DunedinPACE biomarker, al reduceerde de regressie coëfficiënt van de DunedinPACE biomarker met iets minder dan de helft (B= 0.092, p= 1.32E-06). De regressie coëfficiënten kwamen, respectievelijk, overeen met een versnelde veroudering van 4,5 jaar en een toegenomen tempo van veroudering van 34 dagen, bijna 5 weken, in 1 chronologisch jaar.

Tabel 7.3. GEE analyses in de gehele steekproef kijkend naar de associatie tussen slachtofferschap weergegeven met tijdsindicatie en epigenetische leeftijdsversnelling.

Model 1	Hannum			Horvath			PhenoAge			GrimAge			DunedinPACE		
	B	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**
Gewelds misdrijf															
0–5 jaar geleden	-0.196	0.937	0.834	0.265	0.958	0.782	-0.225	1.437	0.875	-0.011	0.975	0.991	-0.027	0.049	0.588
5+ jaar geleden	-0.904	0.508	0.075	-0.598	0.448	0.182	-0.594	0.796	0.456	-0.678	0.566	0.231	-0.025	0.015	0.092
Zedenmisdrijf															
0–5 jaar geleden	**4.311**	**0.995**	**1.47E-05**	1.367	0.523	0.009	**6.988**	**0.456**	**6.06E-53**	**3.714**	**1.099**	**0.001**	**0.164**	**0.010**	**9.00E-60**
5+ jaar geleden	0.040	0.541	0.941	-0.044	0.475	0.927	-0.321	0.804	0.689	0.916	0.609	0.133	0.045	0.021	0.033
Vermogens misdrijf															
0–5 jaar geleden	-0.598	0.502	0.234	-0.084	0.392	0.831	-0.894	0.590	0.130	-0.312	0.495	0.528	-0.004	0.011	0.719
5+ jaar geleden	-0.281	0.521	0.589	0.398	0.360	0.270	-0.177	0.627	0.778	0.297	0.385	0.441	-0.008	0.012	0.542

Model 2	Hannum			Horvath			PhenoAge			GrimAge			DunedinPACE		
	B	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**
Gewelds misdrijf															
0–5 jaar geleden	-0.274	0.839	0.744	0.367	0.970	0.706	-0.001	0.684	0.999	-0.437	0.866	0.614	-0.045	0.039	0.249
5+ jaar geleden	-1.013	0.492	0.040	-0.532	0.442	0.229	0.034	0.550	0.951	-0.137	0.379	0.718	-0.028	0.012	0.022
Zedenmisdrijf															
0–5 jaar geleden	**4.468**	**0.943**	**2.18E-06**	0.901	0.669	0.178	2.244	0.831	0.007	0.273	0.731	0.709	**0.092**	**0.019**	**1.32E-06**
5+ jaar geleden	0.118	0.548	0.830	-0.035	0.479	0.942	-0.555	0.617	0.369	0.234	0.466	0.615	0.037	0.019	0.048
Vermogens misdrijf															
0–5 jaar geleden	-0.600	0.496	0.227	-0.059	0.381	0.876	-0.386	0.406	0.341	-0.103	0.285	0.717	4.98E-04	0.010	0.959
5+ jaar geleden	-0.294	0.518	0.570	0.377	0.353	0.286	-0.103	0.428	0.809	-0.039	0.238	0.870	-0.017	0.010	0.085

Tabel 7.4 geeft de resultaten weer voor dezelfde modellen als hierboven genoemd, maar dan voor ooit slachtofferschap en apart voor polyvictimisatie. Voor polyvictimisatie waren er zowel in model 1 als 2 geen significante verbanden met de bekeken epigenetische biomarkers. Kijkend naar het ooit meemaken van slachtofferschap lieten vermogensmisdrijven wederom geen significante verbanden zien met de epigenetische biomarkers. In model 1, waarin alleen werd gecorrigeerd voor leeftijd, geslacht en technische covariaten, was er een significant negatief verband met het ooit meemaken van een geweldsdelict en de DunedinPACE biomarker (B= -0.039, p= 0.004). Dit verband viel weg in model 2. Verder waren er in model 1 positieve verbanden tussen het ooit hebben meegemaakt van een zedenmisdrijf en zowel de GrimAge (B= 1.344, p= 0.004) als de DunedinPACE biomarker (B= 0.051, p= 2.12E-04). Dit komt overeen met respectievelijk een verhoogde biologische leeftijd van 1 jaar volgens de GrimAge biomarker, en een versnelling van respectievelijk 19 dagen, 2.5 week, in 1 chronologisch jaar volgens de DunedinPACE biomarker. Echter, de sterkte van dit verband met de GrimAge biomarker werd zeer sterk gereduceerd en de significantie viel weg na de additionele correctie voor rookgedrag, BMI en de proportie witte bloedcellen. Het ooit meemaken van een zedendelict liet na additionele correctie nog steeds een significant positief verband zien met de DunedinPACE biomarker (B= 0.040, p= 3.53E-04), overeenkomend met een versnelling van respectievelijk 15 dagen, 1 week, in 1 chronologisch jaar.

Discordante tweeling-analyse

Tabel 7.5 laat de resultaten zien van de discordante tweeling-analyses voor de GrimAge en DunedinPACE biomarkers. De overige biomarkers lieten net als in de analyse in de gehele steekproef geen significante verbanden zien. Er waren 170 MZ tweeling paren discordant voor type slachtofferschap en 207 paren discordant voor het aantal delicten. Net als in de gehele sample liet polyvictimisatie geen significant verband zien met de epigenetische biomarkers. Kijkend naar ooit slachtofferschap werden in de MZ discordante paren analyses werden geen significante associaties gevonden. In model 1 werden de regressie coëfficiënten voor zedenmisdrijven met de GrimAge (B= 0.151, p= 0.768) en de DunedinPACE (B= 0.032, p= 0.032) biomarker gereduceerd in vergelijking

Tabel 7.4. GEE analyses in de gehele steekproef kijkend naar de associatie tussen slachtofferschap ooit meegemaakt, polyvictimisatie en epigenetische leeftijdsversnelling.

		Hannum			Horvath			PhenoAge			GrimAge			DunedinPACE		
		B	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**
Model 1	Geweldsmisdrijf	-0.580	0.454	0.202	-0.108	0.357	0.763	-0.493	0.607	0.417	-1.115	0.428	0.009	**-0.039**	**0.014**	**0.004**
	Zedenmisdrijf	0.897	0.493	0.069	-0.079	0.391	0.839	0.782	0.687	0.255	**1.344**	**0.464**	**0.004**	**0.051**	**0.014**	**2.12E-04**
	Vermogensmisdrijf	-0.361	0.356	0.311	0.237	0.271	0.383	-0.306	0.451	0.497	-0.051	0.294	0.863	-0.010	0.009	0.260
Model 2	Geweldsmisdrijf	-1.024	0.488	0.036	-0.026	0.354	0.941	0.321	0.455	0.480	-0.431	0.287	0.133	-0.030	0.011	0.007
	Zedenmisdrijf	1.052	0.557	0.059	-0.187	0.396	0.637	-0.204	0.534	0.702	0.512	0.309	0.097	**0.040**	**0.011**	**3.53E-04**
	Vermogensmisdrijf	-0.489	0.373	0.189	0.275	0.266	0.301	-0.037	0.314	0.906	-0.008	0.179	0.965	-0.010	0.007	0.168

		Hannum			Horvath			PhenoAge			GrimAge			DunedinPACE		
		B	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**
Model 1	Polyvictimisatie	-0.047	0.121	0.699	-0.026	0.095	0.782	-0.099	0.166	0.549	0.144	0.095	0.129	-0.001	0.003	0.679
Model 2	Polyvictimisatie	-0.056	0.120	0.644	-0.007	0.095	0.941	-0.019	0.127	0.880	0.041	0.071	0.569	-0.003	0.003	0.318

NB: B= regressiecoëfficiënt, SE= standaardfout, p= p-waarde. Significante verbanden zijn dikgedrukt (<0.006). Model 1 corrigeerde voor leeftijd, geslacht en technische covariaten. Model 2 corrigeerde additioneel voor rookgedrag, BMI en proportie witte bloedcellen. Voor de Hannum biomarker is niet gecorrigeerd voor de proportie witte bloedcellen, omdat deze biomarker expliciet rekening houdt met de witte bloedcel compositie in de berekening van biologische leeftijd.

Tabel 7.5. Resultaten van de discordante tweeling-analyse, kijkend naar de associatie tussen slachtofferschap ooit meegemaakt, polyvictimisatie en epigenetische leeftijdsversnelling.

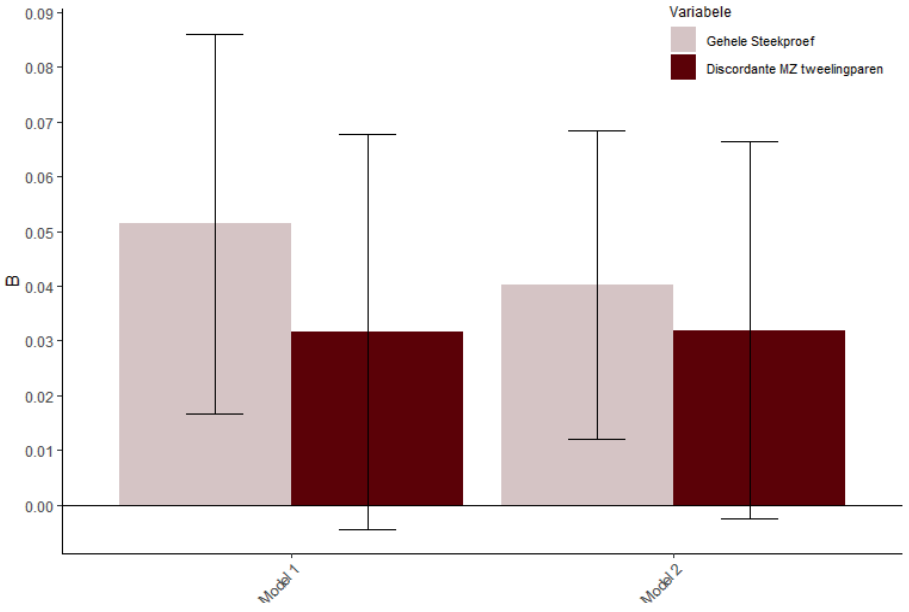
		Hannum			Horvath			PhenoAge			GrimAge			DunedinPACE		
		B	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**	**B**	**SE**	**p**
Model 1	Geweldsmisdrijf	-0.443	0.693	0.525	-0.241	0.432	0.579	-0.661	0.796	0.410	-0.298	0.547	0.588	0.004	0.018	0.810
	Zedenmisdrijf	0.481	0.600	0.426	0.501	0.367	0.176	0.540	0.727	0.461	0.151	0.509	0.768	0.032	0.014	0.032
	Vermogensmisdrijf	-0.060	0.286	0.834	0.232	0.193	0.231	-0.591	0.394	0.137	0.208	0.257	0.420	-0.002	0.008	0.749
Model 2	Geweldsmisdrijf	-0.501	0.715	0.486	-0.088	0.473	0.852	-0.068	0.510	0.894	0.187	0.370	0.615	0.016	0.015	0.288
	Zedenmisdrijf	0.265	0.706	0.709	0.739	0.433	0.094	0.757	0.548	0.173	-0.114	0.441	0.796	0.032	0.014	0.024
	Vermogensmisdrijf	0.008	0.296	0.980	0.379	0.192	0.051	-0.294	0.233	0.209	-0.072	0.170	0.673	-0.004	0.007	0.577

		Hannum			Horvath			PhenoAge			GrimAge			DunedinPACE		
		B	**SE**	**p**	**B**		**p**	**B**		**p**	**B**		**p**	**B**		**p**
Model 1	Polyvictimisatie	-0.137	0.196	0.484	0.040	0.134	0.764	-0.342	0.250	0.174	0.071	0.164	0.665	0.002	0.005	0.735
Model 2	Polyvictimisatie	-0.072	0.216	0.739	0.126	0.133	0.342	-0.171	0.152	0.262	-0.046	0.112	0.679	0.002	0.004	0.657

NB: B= regressiecoëfficiënt, SE= standaardfout, p= p-waarde. Significante verbanden zijn dikgedrukt (<0.006). Model 1 corrigeerde voor leeftijd, geslacht en technische covariaten. Model 2 corrigeerde additioneel voor rookgedrag, BMI en proportie witte bloedcellen. Voor de Hannum biomarker is niet gecorrigeerd voor de proportie witte bloedcellen, omdat deze biomarker expliciet rekening houdt met de witte bloedcel compositie in de berekening van biologische leeftijd.

met de eerder gevonden associaties in de gehele steekproef (respectievelijk, B= 1.344 en B= 0.051). Het afnemen van de regressie coëfficiënt in model 1 in discordante tweelingen suggereert dat het verband gedeeltelijk verklaard wordt door gedeelde omgevings- en/of genetische factoren.

In model 2 was de regressiecoëfficiënt voor zedenmisdrijven en DunedinPACE vergelijkbaar met de gehele steekproef (B= 0.032, p= 0.024 en B= 0.040, p= 3.53E-04, respectievelijk). Figuur 3 illustreert de vergelijking tussen de analyse in de gehele steekproef en de discordante tweeling-analyse voor zedenmisdrijven en de DunedinPACE biomarker. Het patroon suggereert dat het verband slechts voor een gedeelte kan worden verklaard door gedeelde omgevings- en genetische factoren, maar de vergelijkbare effecten in beide analyses wijzen erop dat er mogelijk sprake is van een causaal verband tussen slachtofferschap van zedenmisdrijven en versnelling van de biologische veroudering, zoals gemeten door de DunedinPACE biomarker. Het feit dat



Figuur 7.3. Resultaten GEE gehele steekproef en discordante MZ tweeling-analyse voor het ooit meemaken van een zedenmisdrijf en de DunedinPACE biomarker. NB: B= regressiecoëfficiënt. Model 1 is gecorrigeerd voor technische covariaten in beide analyses, en leeftijd en geslacht in de gehele steekproef. Model 2 corrigeerde additioneel voor BMI, rookgedrag en witte bloedcellen.

deze associaties in de MZ-tweelinganalyse niet significant zijn, kan deels worden toegeschreven aan de kleinere statistische power van deze subgroep.

Discussie

Dit is een van de eerste studies die een relatie onderzocht bij volwassenen tussen verschillende soorten slachtofferschap en epigenetische leeftijdsversnelling. We maakten gebruik van een grote, uit de algemene populatie afkomstige, steekproef van families uit het Nederlandse Tweelingenregister en onderzochten vijf verschillende epigenetische biomarkers: Hannum, Horvath, PhenoAge, GrimAge en DunedinPACE. In deze steekproef vonden we geen verband tussen het meemaken van vermogens- of geweldsmisdrijven en biologische veroudering. Recent slachtofferschap van zedenmisdrijven lijkt echter wel gerelateerd aan biologische leeftijdsversnelling met respectievelijk 4, 7 en 4 jaar volgens de Hannum, PhenoAge en GrimAge biomarkers en een toegenomen tempo van veroudering van 60 dagen in 1 chronologisch jaar volgens de DunedinPACE biomarker.

Na additionele correctie voor de proportie witte bloedcellen, BMI en rookstatus, reduceerde het verband sterk en was dit niet meer significant voor de PhenoAge en GrimAge biomarkers. Dit suggereert dat de waargenomen versnelling van biologische veroudering, zoals gemeten door de PhenoAge en GrimAge biomarkers, deels verband houdt met bredere levensstijlfactoren en wijst op een complex samenspel tussen slachtofferschap, leefstijl en biologische factoren. Zo kan het zijn dat rookgedrag of BMI verandert als reactie op het slachtofferschap (Budenz, Klein, & Prutzman, 2021; Konkolÿ Thege et al., 2017). Deze veranderingen kunnen op hun beurt de primaire aanjagers zijn van de waargenomen epigenetische veranderingen, zoals geïmpliceerd door de afname in significantie na correctie voor deze factoren bij de PhenoAge en GrimAge biomarkers. Daarnaast is het mogelijk dat bepaalde kenmerken, zoals impulsiviteit, lage zelfcontrole of een lager IQ, die samenhangen met roken en een hoog BMI, ook de kans op slachtofferschap vergroten. Dit zou kunnen verklaren waarom de aanvankelijke verbanden verdwijnen na correctie voor deze leefstijlfactoren. Hetzelfde geldt voor schommelingen in het proportie witte bloedcellen, wat een proxy is voor gezondheid en

ontstekingsprocessen. Slachtofferschap kan mogelijk leiden tot veranderingen in proporties witte bloedcellen, wat vervolgens de relatie tussen slachtofferschap en biologische veroudering beïnvloedt. Eerder onderzoek heeft aangetoond dat aandoeningen zoals angst en depressie, die vaak voortkomen uit traumatische ervaringen, geassocieerd zijn met verhoogde ontstekingsmarkers (Maes, 2011). Deze ontstekingsprocessen kunnen bijdragen aan epigenetische aanpassingen die de veroudering versnellen (Franceschi & Campisi, 2014).

Desalniettemin hield het verband tussen het recent meemaken van een zedendelict en zowel de Hannum als de DunedinPACE biomarker na additionele correctie stand; voor de Hannum biomarker een epigenetische veroudering van bijna 4.5 jaar, voor de DunedinPACE een verhoogd tempo van veroudering overeenkomstig met 34 dagen in 1 chronologisch jaar. Daarmee zien we een robuuste link tussen slachtofferschap van zedendelicten en biologische leeftijdsversnelling, overeenkomend met eerder onderzoek naar stressvolle levensgebeurtenissen (Marini et al., 2020; Tang et al., 2020), en negatieve jeugdervaringen en partnergeweld (Bourassa et al., 2020; McCrory et al., 2022; Suglia et al., 2022). Mogelijk worden de directe effecten van slachtofferschap gemedieerd door stressmechanismen. Bekend is dat chronische stress kan leiden tot disregulatie van de hypothalamus-hypofyse-bijnier (HPA) (Heim et al., 2008; Nikkheslat et al., 2020), wat resulteert in verlaagd cortisol (Meewisse et al., 2007), wat weer epigenetische verandering kan veroorzaken (Jiang et al., 2019; Labonte et al., 2014). Echter, voor niet recent meegemaakte zeden delicten vonden we g een significant verbande met epigenetische leeftijdsversnelling. Dit suggereert enig herstel na slachtofferschap.

Wij vonden geen verband tussen polyvictimisatie en de diverse epigenetische biomarkers, wat niet in lijn is met eerder onderzoek (Belsky et al., 2022; Kim et al., 2023), mogelijk omdat wij slechts naar 3 typen delicten hebben gekeken. Kijkend naar het ooit hebben meegemaakt van een delict, was er een verband tussen biologische veroudering en zedenslachtofferschap, al was het verband minder sterk dan bij het recent meemaken van een zedenmisdrijf. Dit suggereert enig herstel na slachtofferschap.

Onze studie probeerde zoveel mogelijk confounding van verbanden uit te sluiten door het gebruik van een discordante MZ tweelinganalyse, waarmee we konden controleren voor gedeelde omgeving en genetische factoren. Hoewel er geen significante verbanden meer werden gevonden tussen de epigenetische biomarkers en slachtofferschap, nam de effect grootte van het verband nauwelijks af. Dit suggereert dat de verbanden die in de gehele steekproef waren gevonden, maar beperkt beïnvloed worden door gedeelde omgevings- en genetische factoren. En daarmee dat het verband tussen slachtofferschap van zedenmisdrijven en versnelling van de biologische veroudering, zoals gemeten door de DunedinPACE biomarker, mogelijk causaal is. Het ontbreken van significantie in de discordante MZ-tweelinganalyse kan deels worden toegeschreven aan de kleinere steekproefgrootte en daarmee een verminderde statistische power.

Ondanks een aantal sterke punten heeft onze studie ook beperkingen. Ten eerste, hoewel onze steekproefgrootte groter was dan die van eerdere studies naar slachtofferschap en versnelde veroudering, was het aantal recent gerapporteerde misdrijven beperkt. We konden daarom niet kijken naar het recent meemaken van een zedendelict in de discordante tweeling analyse. Ten tweede speelt de subjectieve aard van hoe individuen slachtofferschap ervaren en rapporteren een rol (Kessler & Wethington, 1991; Van de Mortel, 2008). Zo kan de betekenis van een delict sterk variëren; de een vindt de diefstal van een telefoon mogelijk niet significant genoeg om te melden, terwijl een ander dat wel doet. Hoewel men ook zou kunnen stellen dat de subjectieve ervaring belangrijker is dan de objectieve ernst van de gebeurtenis, blijft deze subjectiviteit een uitdaging bij het standaardiseren en vergelijken van ervaringen tussen individuen. Daarbovenop was er, naar we moeten aannemen, aanzienlijke variabiliteit in de ernst van incidenten binnen dezelfde categorie. Zowel woninginbraak als zakkenrollerij valt onder vermogensdelicten, en zo ook aanranding en ernstige verkrachting onder zedendelicten. Het is mogelijk dat als we homogene soorten slachtoffergroep hadden onderzocht, de verbanden met ernstigere delicten dan sterker waren geweest. Verder is ook de specifieke leeftijd waarop slachtofferschap plaatsvond van belang, maar hadden wij daar geen goede maat voor gezien onze gebruikte categorisering in korter en langer dan vijf jaar geleden: wij konden zo niet zien of delicten

bijvoorbeeld in de vroege kindertijd hadden plaatsgevonden, zie over het belang daarvan bijvoorbeeld: Jovanovic et al. (2017); Marini et al. (2020); Tang et al. (2020). Tot slot heeft het gebruik van gegevens over discordante MZ-tweelingen grote voordelen, maar onderzoeken we een bijzondere groep mensen, bij wie men allereerst mag verwachten dat bij slachtofferschap van de een, ook een invloed zal hebben op de co-tweeling die geen slachtoffer is geweest en in methodologische zin mogelijk ook een deel van het slachtofferschap 'meekrijgt'. Dat betekent dat de effecten van slachtofferschap onderschat zouden worden. Ook mag men verwachten dat eeneiige tweelingen, die soms een bijzondere band hebben, mogelijk op meer opvang en steun kunnen rekenen dan men van een gewone broer of zus zou krijgen, wat de impact van het delict kan verzachten. Dat zou betekenen dat we in deze bijzondere groep, daardoor mogelijk minder grote effecten zien dan in een groep niet-eeneiige tweelingen.

Onze studie laat zien dat slachtofferschap van zedendelicten, zowel recent als ooit, geassocieerd is met epigenetische leeftijdsversnelling en dat dergelijke ervaringen mogelijk langdurige, ook biologische, gevolgen hebben. Toekomstig onderzoek moet zich richten op het verfijnen van de zelfrapportage van slachtofferschap, waarbij rekening wordt gehouden met de ernst, frequentie en timing van incidenten om de complexe relaties tussen slachtofferschap, levensstijl, genetica en biologische veroudering beter te begrijpen. Het is te verwachten dat de waargenomen epigenetische leeftijdsversnelling implicaties heeft voor de lange termijn gezondheid van slachtoffers van zedendelicten. Het is bekend dat verhoogde epigenetische leeftijdsversnelling geassocieerd is met een hoger risico op chronische ziekten zoals hart- en vaatziekten, kanker en cognitieve achteruitgang. Daarom onderstrepen onze bevindingen het belang van vroegtijdige interventies en ondersteuning voor slachtoffers, met als doel de mogelijke negatieve gezondheidseffecten op de lange termijn te beperken.

7

Chapter 8.

General Summary and Discussion

General Summary

The research presented in this dissertation investigated the complex relationship between victimization and its impacts on mental health, physical health, and biological aging. Utilizing data from the Netherlands Twin Register, this research employed the Co-Twin Control Design (CTCD) and sought to disentangle the effects of victimization from genetic and shared environmental factors, in order to better understand the true consequences of crime victimization.

The Co-Twin Control Design: A Methodological Foundation

The dissertation began with a methodological exploration of the CTCD in **Chapter 2**, focusing on its application in large twin registries. This chapter presents an overview of the CTCD, discussing its application to both binary and continuous exposures and outcomes. It includes simulation analyses conducted in R, alongside analysis scripts in SPSS, R, and STATA, to explore various confounding scenarios.

The CTCD is particularly effective when investigating causal relationships where genetic and shared environmental confounders are of concern. In such contexts, the CTCD is applied to monozygotic (MZ) twins who are discordant for the exposure of interest—such as victimization. Since MZ twins are genetically identical and share the same prenatal and familial environments, they are inherently matched for genetic factors, shared environmental influences, age, and sex. This matching controls for confounding variables that are often unmeasured or unobservable, allowing for a clearer attribution of differences in outcomes to the exposure (victimization) itself. The inclusion of dizygotic (DZ) twins in the CTCD adds another dimension to the analysis. While DZ twins share the same shared environment, they are not genetically identical. Comparing discordant DZ twins provides additional insights about the source of confounding, but does not offer the same level of control for genetic confounding as MZ twins.

The CTCD thus serves as a robust methodological approach for disentangling causal effects in the presence of genetic and shared environmental confounding. By leveraging the unique characteristics of twin pairs — particularly monozygotic twins — this design

enhances the validity of the findings and contributes to a more nuanced understanding of the consequences of victimization.

Victimization and Mental Health: The Role of Familial Factors

The relationship between crime victimization and mental health outcomes, i.e. depression, anxiety, and loneliness, is explored in depth in **Chapter 3**. Through the analysis of data from 19,867 individuals in Dutch twin families, this chapter reveals that victimization, particularly from violent and sexual crimes, is strongly associated with negative mental health outcomes. However, CTCD analyses suggested that these associations may not be causal. Familial factors, including genetic predispositions, contribute to the association between victimization and mental health outcomes. This result highlights the importance of greater awareness of the role of shared genetic and environmental influences on outcome and exposure when investigating the consequences of victimization, and highlight the value of genetically informative study designs that can take this into control. By including longitudinal data into the analyses, I found that victims of sexual and violent crimes already show elevated mental health problems before victimization, suggesting that individuals with more mental health issues and loneliness may be at higher risk of such victimization.

The Role of Social Support: Genetic Influences and Protective Effects

Chapters 4 and 5 delved into the dual nature of social support, examining both its genetic basis and its role as a protective factor against adverse effects of crime victimization. Analyzing data from 8,019 adult twins, **Chapter 4** estimated that approximately 37% of the variance in social support is attributable to genetic factors, challenging the notion that social support is solely an environmental construct and highlighting its complexity as shaped by both genetic and environmental influences. While the genetic contribution is significant, non-shared environmental factors account for 63% of the variance in social support.

Chapter 5 tested how social support influences both general and mental health outcomes following victimization by testing both a main effect of social support (i.e., its direct association with health outcomes) and a moderation effect (i.e., whether social

support buffers or reduces the negative impact of victimization on health outcomes). Lower levels of social support were associated with poorer general health and increased levels of depression. Victimization was significantly associated with poorer health outcomes, with sexual crimes having the strongest association. In addition to these main effects, social support also played a moderating role, buffering the negative effects of victimization. Specifically, the adverse mental health impacts of victimization of violent and sexual crimes were less severe for those with higher social support compared to those with lower levels of support. This suggests that social networks may help mitigate the trauma of victimization by offering emotional and practical resources. The CTCD analyses supported a causal relationship of social support on depression across all discordant twin comparisons. However, the buffering effect of social support following victimization was found to be confounded by genetic and shared environmental factors.

Epigenetics and Biological Aging: The Impact of Life Events and Victimization

The last part of the dissertation investigated the impact of negative life events (**Chapter 6**) and victimization (**Chapter 7**) on biological aging as indexed by epigenetic biomarkers. In **Chapter 6**, a series of different epigenetic biomarkers, namely Hannum, Horvath, PhenoAge, GrimAge and DunedinPACE were investigated. These are moderately correlated among themselves and thus each offer a unique view on epigenetic consequences. Notably, the majority of participants had experienced more than one negative life event, indicating that cumulative life stressors, rather than isolated incidents, are common. Experiencing a higher number of negative life events were associated with accelerated epigenetic aging, as measured by the GrimAge biomarker. When examining specific life events, financial problems and sexual victimization were associated with age acceleration of approximately 1.6 years and 1.1 years, respectively, according to the GrimAge biomarker. Financial problems were also linked to an increased pace of aging, roughly 10 days per year, as measured by the DunedinPACE biomarker. Additionally, job loss was associated with an increase of 0.87 years in age acceleration, according to the GrimAge biomarker.

After controlling for factors that are known to be associated with epigenetic biomarkers, such as BMI, smoking habits, and white blood cell proportion, the association at the population level between the total number of life events and financial problems and epigenetic age acceleration persisted for the GrimAge biomarker. In the discordant twin analyses, these associations were significantly reduced when genetic and shared environmental factors were controlled for, suggesting a complex interplay between genetics, environment, and lifestyle in influencing epigenetic aging.

Focusing more closely on victimization experiences, **Chapter 7** demonstrated that recent experiences of sexual victimization (i.e., experienced less than 5 years ago) were associated with epigenetic age acceleration of respectively 4, 7, and 4 years according to the Hannum, PhenoAge, and GrimAge biomarkers, and an increase in the pace of aging by 60 days per year according to the DunedinPACE biomarker. On the other hand, weaker effects were observed for life-time experiences of sexual victimization, which were associated with an increase of 1 year according to the GrimAge biomarker and an increase pace of aging by 19 days per year as measured by the DunedinPACE biomarker.

The association between recent sexual crime victimization and the Hannum and DunedinPACE biomarkers remained significant, with only slight reductions, after adjusting for confounding factors such as BMI and smoking. Similarly, the association between lifetime sexual victimization and the DunedinPACE biomarker also remained significant. Although the MZ discordant twin analyses do not yield significant associations, the effect size was only slightly reduced when compared to the association in the full sample, suggesting that the association between sexual victimization and epigenetic age acceleration may be partly causal.

Collectively, the research presented in this dissertation demonstrates the association of crime victimization with individuals' mental health and biological aging, that were especially marked for victims of sexual crime victimization. Victims of sexual crimes exhibited higher levels of depression, anxiety, loneliness, and also showed accelerated epigenetic aging. By employing the CTCD, this work offers a clearer understanding of

these complex relationships and sets the stage for future research aimed at further exploring the mechanisms underlying the impacts of crime victimization.

General Discussion

This dissertation advances our understanding of the complex relationships between crime victimization, mental health, and biological aging. By employing the Co-Twin Control Design (CTCD), the dissertation provides new insights into causality versus correlation, examines multiple types of victimization, and explores the biological underpinnings through epigenetic markers. In this discussion, I will first delve into how these findings **contribute to the existing literature on crime victimization and health**. Then, I will reflect on the strengths and limitations of the **methodology**, to provide a broader context for interpreting the findings and guiding future research directions.

Impact of Victimization: the Invisible Scars

Research on victimization has extensively explored the physical and psychological consequences of victimization. This dissertation specifically investigates the psychological and biological impacts, focusing on mental health challenges and increased epigenetic aging. Victims may suffer from consequences that are not immediately evident to the outside world, such as depression, anxiety, and epigenetic changes. These "invisible scars" can lead to significant impairments in quality of life, as victims grapple with internal struggles. In this discussion, I will examine how my findings contribute to the existing literature by addressing a key theme of the distinction between causality and correlation. My research highlights the importance of considering multiple types of victimization, such as sexual, violent, and property crimes. Furthermore, I expand the conversation to include the role of epigenetics in establishing the relationship between victimization can lead to accelerated epigenetic aging.

Victimization, Mental Health, and the Role of Familial Factors

The findings in this dissertation reaffirm that victimization, particularly of violent and sexual crimes, is strongly associated with negative mental health status such as depression, anxiety, loneliness, and self-reported poor health. The findings from the CTCD provide important new insights by suggesting that familial factors, including genetic predispositions, confound the relationship between victimization and mental health consequences. These results provide nuances regarding the causal nature of

victimization and mental health outcomes. Previous research firmly established associations which served as an important first step. Based on these findings, my next step was accounting for familial confounding factors. This dissertation underscores the importance of incorporating genetic predispositions and shared environmental influences into theoretical models of victimization and mental health.

This dissertation demonstrates that individuals with pre-existing mental health problems have a greater chance of becoming victims of crime. This is consistent with criminological theory positing that offenders preferably target individuals in more vulnerable situations, and it shows the importance of recognizing that victimization disproportionately affects those who are already vulnerable for poor mental health outcomes, further exacerbating their vulnerability (Khalifeh et al., 2015; Krahé & Berger, 2017; Latalova, Kamaradova, & Prasko, 2014; Monahan et al., 2017; Rossa-Roccor, Schmid, & Steinert, 2020). Vulnerability to victimization is thus not just about being in the wrong place at the wrong time; it may also be linked to deeper, pre-existing mental health and familial factors. This shows that many victims do not experience victimization, and negative live events in general, in isolation. An important finding in my dissertation is that it often occurs alongside other negative life events, i.e. victimization is not always an isolated, random event, but may be part of a broader pattern of exposure to stress and trauma. This reinforces the idea that genetic and environmental vulnerabilities can place some individuals at greater risk for multiple negative life events (Middeldorp et al., 2005).

These findings emphasize the need for a shift in practical approaches to victim support and crime prevention. Recognizing that certain individuals are at a greater risk of becoming victims of crime suggests that prevention and intervention programs should also focus on effectively targeting high-risk groups, such as those experiencing mental health problems. Moreover, since genetic predispositions to mental health problems can increase susceptibility to victimization, family members who share these genetic factors may also be at elevated risk for both mental health issues and victimization. Thus, vulnerability to victimization may cluster within families due to shared genetics and

environmental influences. Recognizing this familial risk underscores the importance of including family members in prevention and intervention efforts. By providing support not only to individuals but also to their family members, we can more effectively address the underlying vulnerabilities that contribute to the cycle of victimization and mental health problems. Furthermore, since victims themselves are at a high risk for mental health problems, organizations that support them should prioritize addressing these concerns in their assistance, regardless of whether the mental health problems are caused by the victimization or not.

Social Support

An important factor that may buffer the impact of victimization and these pre-existing vulnerabilities is social support. In this dissertation, I found that higher levels of social support were associated with better mental health outcomes and improved self-reported health, consistent with the broader literature on social support as a protective factor against psychological distress (Harandi, Taghinasab, & Nayeri, 2017; Holt & Espelage, 2005; Scarpa, Haden, & Hurley, 2006). Social support also played a moderating role, buffering the negative effects of victimization. Specifically, the adverse mental health impacts of victimization, particularly violent and sexual crimes, were less severe for those with higher social support compared to those with lower levels of support. This suggests that help, such as offered by victim support organizations and individual social networks, may help mitigate the trauma of victimization by offering emotional and practical resources.

Genetic Influences on Social Support, Life Events and Victimization

In this dissertation, I also found that social support itself is a partly heritable trait. This leads to a broader reconsideration of what we classify as environmental factors. While social support is often viewed as an external influence, the findings in this dissertation indicate that it is shaped by underlying genetic factors as well. This challenges the tendency to automatically label social support—and similar factors—as purely environmental. Previous research has also shown that many traits traditionally thought of as environmental can have significant genetic components (Plomin & Bergeman, 1991; Vinkhuyzen et al., 2010).

The concept that so-called environmental factors are not random and influenced by genetic factors also extends to negative life events, such as victimization (Beaver et al., 2009; Johnson et al., 2013). Middeldorp et al. (2005), previously found that genetic influences contribute to the occurrence of certain life events (i.e., serious illness self, or other, death of other, divorce, accident and robbery). Although the heritability estimates for these life events are not extremely high, they warrant consideration. Similarly, Beaver et al. (2009) found that genetic factors explain between 40% and 45% of the variance in adolescent victimization, indicating a substantial genetic influence on the likelihood of being victimized during adolescence. These findings highlight the importance of reevaluating how we conceptualize environmental risk factors in the context of victimization. Instead of viewing them as solely external, it is important to recognize the interplay between genetics and environmental influences.

Overall, this further emphasizes the necessity of integrating genetically informed designs not only into the study of the consequences of victimization but also into social science research as a whole. By accounting for genetic influences, researchers can more accurately assess causal relationships and develop more effective intervention strategies that address both environmental and genetic factors contributing to victimization and mental health problems.

Epigenetic Aging

My dissertation offers new insights into the relationship between negative life events overall, and specifically crime victimization, and biological aging. The results for epigenetic markers, such as those measured by the GrimAge biomarker, reveal that the cumulative experience of negative life events can leave biological marks associated with accelerated aging. This underscores the importance of considering cumulative exposure to life stressors, as certain individuals and groups are more likely to experience multiple negative life events over time. The literature consistently shows that these individuals not only face higher levels of stress but also accumulate multiple life stressors throughout their lives (Nurius, LaValley, & Kim, 2020; Reiss et al., 2019). This

accumulation significantly amplifies the biological toll, as repeated exposure to stress accelerates the aging process more than most of the single events do.

When considering specific negative life events, the findings in this dissertation highlight that various types of stressors, namely financial problems and sexual crimes, are associated with accelerated biological aging. Financial difficulties showed a robust association with accelerated aging even after additional corrections for confounders, such as BMI, smoking and educational attainment. This emphasizes the need for interventions aimed at alleviating economic burdens. By focusing on lessening financial stress, these policies might contribute to mitigating the accelerated aging associated with such stressors.

For sexual crime victimization, the findings reveal a more nuanced picture. Initially, when I analyzed the lifetime victimization to sexual crimes, my conclusion was that the association between sexual crime victimization and biological aging disappeared after controlling for factors such as lifestyle behaviors (e.g., smoking) and variations in BMI, and white blood cell counts. This suggests that lifestyle factors may act as confounding variables in the relationship between sexual crime victimization and biological aging. Individuals with unhealthy lifestyles may have a greater risk of both experiencing victimization and exhibiting accelerated biological aging. For instance, engaging in risky behaviors associated with unhealthy lifestyles might increase exposure to environments where victimization is more likely, while simultaneously contributing to faster biological aging through direct physiological effects.

Alternatively, these lifestyle factors may also mediate the relationship by being altered in response to the experience of sexual crime victimization. For example, the stress of the event might lead victims to engage in maladaptive coping strategies, such as increased smoking or unhealthy eating, which in turn could influence biological aging. Additionally, it could mean that fluctuations in white blood cell counts —a proxy for health and inflammatory processes— might mediate the relationship between sexual crime victimization and epigenetic aging. The victimization experience could potentially lead to changes in white blood cell proportions, affecting inflammatory responses that

are crucial in biological aging. Previous research has indicated that conditions such as anxiety and depression, often arising from traumatic experiences, are associated with elevated inflammatory markers (Maes, 2011). These inflammatory processes can contribute to epigenetic modifications that accelerate epigenetic aging (Franceschi & Campisi, 2014).

In subsequent analyses, I expanded my sample size to re-examine the lifetime experience of sexual crime victimization, and also looked at recent victimization (i.e., those occurring within the last five years). In this larger sample, the lifetime experience of a sexual crime victimization was significantly associated with the pace of aging according to the DunedinPACE biomarker, even after the additional corrections. When focusing on recent victimization, the impact on epigenetic aging became even more pronounced. It could be speculated that the association between sexual crime victimization and epigenetic age acceleration, and its persistence after accounting for lifestyle factors and white blood cell counts is possibly mediated by stress mechanisms, although this hypothesis requires further research.

Genetic and Environmental Influences on Life Events, Victimization and Aging

When accounting for genetic and shared environmental factors through MZ discordant twin analyses, the associations with epigenetic aging were partly explained by genetic predispositions and shared environmental influences in the case of cumulative life events. The fact that the association diminished when controlling for familial factors implies that individuals who experience such stressors have underlying genetic or shared environmental vulnerabilities that contribute both to their exposure to negative life events and to accelerated epigenetic aging processes. For instance, genetic factors related to stress response may predispose individuals to both a higher risk of victimization, as heightened stress reactivity may lead to behaviors that can appear as more anxious or vulnerable, and greater susceptibility to biological aging, as prolonged stress elevates cortisol levels, accelerating the aging process through increased wear and tear on the body.

Looking at sexual crime victimization and epigenetic aging, this association was not significant after controlling for genetic and shared environmental factors in the CTCD. Although the effect sizes remained similar to those observed in the full sample, the lack of statistical significance implies that we may not conclusively attribute the accelerated epigenetic aging to sexual crime victimization independently of familial factors. Therefore, while the findings hint at a direct biological impact of sexual victimization, some caution is warranted in interpreting these results. Future research with larger samples and more elaborate measurements, for instance measurements that disaggregate various types of sexual crime victimization or specific timing of the event are needed to confirm whether sexual victimization has direct causal effects on epigenetic aging or if the association is primarily driven by shared familial factors.

Evaluating the Methodological Approaches

As I stated in my introduction, understanding the consequences of victimization is challenging due to the reliance on observational studies, which require large samples with detailed information on both exposures and outcomes. Here I want to discuss the statistical approaches and the choice of epigenetic biomarkers as outcomes. The CTCD provides substantial advantages, particularly because it controls for confounding variables that are often unmeasured or unobservable, allowing for a clearer attribution of differences in outcomes to the exposure itself. However, some methodological considerations must be taken into account when interpreting the findings.

Assumptions Underlying the CTCD

The CTCD is particularly valuable in its ability to control for genetic and shared environmental factors, which often confound traditional observational studies. By leveraging the natural control provided by twins, the CTCD strengthens causal inference by accounting for pre-existing genetic and shared environmental differences that influence both exposure and outcome. This is particularly important because exposures such as victimization are not randomly distributed; there are pre-existing differences between those who are victimized and those who are not, which traditional observational designs may fail to adequately address.

A key assumption for making causal interpretations based on the CTCD is the absence of confounding by unmeasured non-shared (environmental) factors. While the CTCD effectively controls for genetic and shared environmental influences, it assumes that unique individual exposures—such as different friendships, work environments, or stressful events—do not independently influence both the exposure (e.g., victimization) and the outcomes of interest (e.g., mental health or biological aging). Research by Frisell et al. (2012) emphasizes that within-pair estimates in the CTCD may be more prone to bias from non-shared confounders than traditional unpaired estimates. This occurs when twins differ more in unmeasured non-shared confounding factors than in the exposure of interest, potentially leading to greater bias in the within-pair comparison. Bias introduced by non-shared confounders can lead to either over- or underestimation of the causal effect. If the non-shared factors influence both the exposure and the outcome in the same direction (e.g., increasing both the likelihood of victimization and mental health issues), the positive association between victimization and mental health problems may be overestimated. Conversely, if they act in opposite directions, the effect may be underestimated.

While it is essential to acknowledge the potential for bias due to non-shared confounders, the existing evidence indicates that the association between stressful life events and mental health outcomes is largely influenced by genetic factors rather than non-shared environmental factors. For instance, Boardman et al. (2011) conducted a bivariate Cholesky decomposition to examine the relationship between stressful life events and depression. They found that approximately 55% of the correlation between stressful life events and depression was due to common genetic factors influencing both traits, while the remaining 45% was attributed to shared environmental influences. Non-shared environmental factors did not play a significant role in the association. This suggests that genetic factors are a substantial source of the observed relationship, and the influence of non-shared environmental confounders is limited.

Furthermore, in our analyses, we observed that the positive association between victimization and mental health outcomes was attenuated when controlling for genetic

and shared environmental factors, suggesting that confounding is present. Given that many non-shared confounders —such as personality traits or unique stressors— are likely to increase both the risk of victimization and adverse mental health outcomes, the possible bias introduced by these factors would more plausibly lead to an overestimation rather than an underestimation of the causal effect. Therefore, even if there is bias due to non-shared confounders, the likelihood of it reversing our conclusions is minimal.

The Spill-Over Effect

Another assumption underlying the CTCD is the absence of interference between twins—that is, one twin's exposure has no causal impact on the co-twin's outcome (Smith et al., 2020). In the context of victimization, this assumption may not always hold true due to the close emotional bonds and shared experiences between twins. For instance, when one twin experiences victimization, the other twin may be indirectly affected through emotional distress, changes in shared environments, or alterations in family dynamics. If such a spill-over effect is present, it can reduce the within-pair differences in outcomes and can lead to an underestimation of the causal effect of victimization in the CTCD.

Assessing spill-over effects requires longitudinal data to track changes over time. By examining the mental health trajectories of both twins before and after the victimization event, we can determine whether the non-victimized twin's outcomes are influenced by their co-twin's experience. Our sample size, however, did not permit us to study changes in the mental health of non-victimized twins from before to after their co-twin's victimization. Nonetheless, we could compare the changes in mental health from before to after victimization for victims and all their family members. Here we found no evidence of a spill-over effect from the victim to their family members. Both victims and their family members showed no significant increase in mental health problems after the victimization had taken place. This suggests that, within our data, interference between twins does not substantially bias the within-pair comparisons in the CTCD.

Measurement Error and Bias

Measurement error in the exposure, which can misclassify discordant pairs as concordant, can attenuate the association between exposure and outcome. This issue is exacerbated in CTCD studies, where the correlation between twins' exposures tends to be higher than in unrelated individuals. As twins often share similar environments and experiences, even small amounts of measurement error can have a disproportionately large effect on the observed associations. Gustavson et al. (2024) conducted a series of simulations to examine bias in the exposure due to measurement error in sibling control models when the observed exposure-outcome association is truly causal. They show that measurement error can lead to underestimating true causal effects, especially when twins share highly correlated exposures. The study highlighted that as exposure reliability decreases and the correlation between siblings' exposure variables increases, the observed association between exposure and outcome becomes falsely weakened. This increases the risk of incorrectly concluding that the association is confounded by familial factors. This issue is especially relevant in MZ twin studies, as MZ twin correlations are typically higher than sibling and DZ twin correlations. Therefore, the bias introduced by measurement error will be amplified if the exposure variables are highly correlated in the MZ twins but measured imperfectly.

In victimization research, measurement error in self-reported victimization is indeed a concern. For example, Averdijk and Elffers (2012) compared self-reported victimization from surveys to official police records. They found that only 35% of reported victimizations in the survey could be traced back to police data within the reference period. While not all victims report crimes to the police, they also discovered that in 48% of cases, respondents did not mention a victimization event in the survey that had been registered in police records. These discrepancies may be due to misinterpretation of survey questions, errors in police reports, underreporting in surveys, or other factors, but it clearly indicates that some events are not consistently reported, remembered or labeled.

In the context of this dissertation, it is unlikely that measurement error alone fully accounts for the non-significant findings in most of the CTCD analyses. While some degree of measurement error may have contributed to weakening the observed associations, the overall consistency in self-reports of sexual and violent victimization suggests that the measurement was relatively reliable. Specifically, only 2.43% of participants who reported being a victim of sexual crime in an earlier survey later reported no such victimization, and only 3.20% gave inconsistent answers regarding violent crimes. It is possible that some instances of victimization were consistently misreported—either omitted or inaccurately reported in both surveys. However, the low discrepancy in self-reports for sexual and violent victimization suggests that major bias due to measurement error is unlikely for these types of crimes. For property crimes, the higher inconsistency (12.67%) indicates that measurement error might have had a more significant impact on analyses involving this type of victimization. However, when examining the unrelated sample, no significant associations were found between property crime victimization and either mental health problems or biological aging. This suggests that the lack of associations may still be influenced by measurement error, but it is not an issue specific to the CTCD. Rather, measurement error in the reporting of property crime may have broadly affected the overall reliability of the exposure variable, regardless of the analytical method used.

Future Directions

Building upon the findings and limitations discussed in this dissertation, several avenues for future research are critical for deepening our understanding of the complex relationship between victimization and its consequences. A primary challenge in victimization research is the measurement of life events and trauma exposure. Data regarding when victimization occurred, how frequently it happened, and the seriousness of the crime are needed for understanding the nuanced impacts of different types of victimization on mental health, biological aging, and other outcomes. Future research should focus on collecting more granular data to capture these factors, enabling researchers to draw clearer conclusions about the timing, frequency, and the impact of

crime victimization. One approach to improving the precision of these measurements is through record linkage, which involves connecting self-reported victimization data with official records, such as police, medical, or legal documents. This approach could provide a more comprehensive and validated dataset, offering insights into discrepancies between self-reports and official records, and helping researchers identify underreporting or misreporting patterns. Record linkage can also enhance the accuracy of the exposure timeline, ensuring that the timing and context of victimization are properly accounted for.

In addition, future research needs to include a wider range of victimization types. This dissertation has primarily examined property crimes, violent crimes, and sexual victimization, but there is considerable variation within these categories that warrants further investigation. For instance, different subtypes of property crimes (e.g., burglary, theft, vandalism), violent crimes (e.g., assault, robbery, domestic violence), and sexual victimization (e.g., harassment, molestation, rape) may have varying psychological and biological impacts. Examining these subtypes individually could reveal more clearer relationships between specific victimization experiences and health outcomes. New and emerging forms of victimization, such as online harassment, identity theft or sextortion, also warrant further investigation. Studies have linked cybercrime victimization to adverse mental health outcomes, including increased anxiety, depression, and stress levels (Copp, Mumford, & Taylor, 2021; Gorissen et al., 2023; Hamby et al., 2020; Islam, Khanam, & Kabir, 2020). However, these studies are often correlational and may be confounded by pre-existing factors. It is imperative for future research to consider potential familial and environmental confounding when examining the impacts of cybercrime victimization.

Expanding the scope of research to encompass different types of consequences of victimization is equally important. Victimization impacts far more than mental and physical health—it can leave other (invisible) scars on relationships, employment or income. By including these outcomes, future research can better capture the full scope of victimization's impact on individuals and society. Understanding the full burden of

victimization would provide a compelling argument for preventive interventions, both for individual well-being and for the broader societal costs

My findings suggest that familial confounding—the influence of shared genetic and environmental factors—is often present in the relationships between victimization and its outcomes. This needs to be a consideration for future research, as it emphasizes the need to apply methods that can account for these confounding influences, such as the CTCD or discordant sibling designs. Although only MZ twin studies fully account for genetic confounding, data on MZ twins may not always be available. In such cases, other family based designs, such as discordant sibling designs, still provide valuable insights (D'Onofrio et al., 2013). Expanding the use of these family-based designs will offer a more nuanced understanding of the true consequences of victimization.

Epigenetic Biomarkers and EWAS

Building on the need for advanced methodologies, future research should also expand the biological measures used to study the effects of victimization. The epigenetic biomarkers—otherwise known as "epigenetic clocks"— I analyzed as a means of examining the biological effects of negative life events and specifically victimization represent summaries of sets of epigenetic probes. Epigenetic clocks are well-established markers of biological aging, that can be interrogated from blood DNA methylation data, validated in large-scale datasets, and offer a practical and reliable method of assessing biological changes. These biomarkers provide valuable insight into the link between negative life events like victimization and biological aging, thus capturing one aspect of the long-term biological consequences of trauma.

One of the advantages of analyzing epigenetic biomarkers is that they summarize epigenetic information into a smaller set of biological markers, so that the researcher does not need to analyze 400.000 or 800.000 variables, but 5 or 6. This makes them a good option when looking at traits that have a relatively low prevalence, such as sexual victimization. However, this also means that the epigenetic biomarkers may not fully capture all epigenetic modifications associated with victimization. They focus on well-defined regions of the epigenome associated with aging, thus they may not fully capture

all epigenetic changes associated with specific exposures. As a result, while epigenetic clocks are useful for assessing overall epigenetic aging, they may miss subtle or unique epigenetic changes directly related to victimization experiences.

To gain a more comprehensive understanding of the epigenetic changes associated with victimization, conducting an Epigenome-Wide Association Study (EWAS) would be beneficial. An EWAS examines the association between an exposure and DNA methylation levels across the entire genome, testing hundreds of thousands of CpG sites to identify epigenetic modifications linked to specific exposures. The first studies have now emerged that conducted EWAS on childhood adversity and adolescent victimization, finding evidence of altered DNA methylation patterns in individuals exposed to these events (Houtepen et al., 2018; Kandaswamy et al., 2021; Sumner et al., 2022). Looking ahead, future research with large samples may benefit from conducting an EWAS to identify specific loci associated with victimization and to determine whether these changes are distinct from other stress-related epigenetic modifications. Such work would offer a more detailed understanding of how trauma affects the epigenome and whether these effects are unique to victimization or shared across different types of stressors.

Pooling data and a Victimization and Life Events Research Consortium

To address the limitations discussed and propel future research, it is essential to consider strategies for increasing sample sizes, such as pooling data from various sources within the Netherlands and internationally. While victimization events are —fortunately— relatively rare we require larger datasets to conduct robust analyses, particularly when examining rare events like specific types of victimization. By combining data, we can enhance statistical power, enabling more precise estimates and the ability to detect effects from rarer events. Of course, pooling data from different sources comes with potential downsides. The meaning and context of various types of victimization events may differ between datasets due to differences in definitions, measurement tools, or cultural contexts. These discrepancies can affect the comparability of data and the

validity of conclusions drawn from combined analyses. Therefore, careful harmonization of variables and consistent definitions are needed when integrating multiple datasets.

In addition to pooling data, establishing a formal *Victimization and Life Events Research Consortium* focused on meta-analyses would be a valuable strategy. This approach has been successful in genetic research and would allow for synthesizing findings from multiple studies to identify overarching trends and effects of victimization on mental health, biological aging, and other outcomes. By replicating our findings across different populations and contexts, we can validate our conclusions and strengthen the evidence base.

Moreover, a formal research consortium would allow us to conduct an EWAS, which would allow us to identify specific DNA methylation changes associated with victimization. EWAS requires large sample sizes because the effects of victimization on DNA methylation are likely subtle and distributed across many sites in the genome. Without sufficient statistical power, smaller studies may miss these associations or falsely detect them due to random variation. This approach goes beyond the use of epigenetic clocks, providing a more comprehensive picture of how victimization leaves biological marks.

Ultimately, pooling data and a research consortium would facilitate interdisciplinary collaboration between researchers from various fields —psychology, genetics, epigenetics, sociology, and economics— providing a holistic view of how victimization affects individuals and society. By pooling resources, expertise, and data, researchers could address a broad range of consequences related to victimization, such as mental health, biological aging, economic burden, and social consequences. Such an effort could be vital in guiding future research, policy development, and interventions aimed at preventing victimization and mitigating its long-lasting scars.

Chapter 9.

Nederlandstalige Samenvatting en Discussie

Algemene samenvatting

In dit proefschrift onderzocht ik de complexe relatie tussen slachtofferschap en de gevolgen daarvan op geestelijke gezondheid, lichamelijke gezondheid en biologische veroudering. Mijn onderzoek maakte gebruik van gegevens uit het Nederlandse Tweelingen Register (NTR) en paste het Co-Twin Control Design (CTCD) toe om de effecten van slachtofferschap te onderscheiden van die van genetische en gedeelde omgevingsfactoren. Hiermee wilde ik de gevolgen van slachtofferschap na misdrijven beter begrijpen.

Het Co-Twin Control Design: Een methodologische basis

Het proefschrift begint met een methodologische verkenning van het CTCD in **hoofdstuk 2**, gericht op de toepassing ervan in grote tweelingregisters. Dit hoofdstuk geeft een overzicht van het CTCD en bespreekt de toepassing ervan voor zowel binaire als continue variabelen. Dit hoofdstuk bevat simulatieanalyses uitgevoerd in R, en daarnaast scripts in R, SPSS en STATA om scenario's met verschillende maten van 'confounding' te onderzoeken. Confounding verwijst naar de situatie waarin de relatie tussen twee variabelen wordt beïnvloed door een derde variabele, wat het trekken van conclusies over causaliteit bemoeilijkt.

Het CTCD is vooral effectief bij het onderzoeken van causale verbanden waarbij genetische en gedeelde omgevingsfactoren een rol spelen. In een dergelijke context wordt het CTCD toegepast op eeneiige, oftewel monozygote (MZ), tweelingen die discordant zijn voor een specifieke blootstelling, zoals slachtofferschap. Dit betekent dat de ene tweelingbroer of -zus wel slachtoffer is geworden van een misdrijf, terwijl de andere dat niet is. Aangezien eeneiige tweelingen genetisch identiek zijn en dezelfde prenatale en familiare omgeving (de gedeelde omgeving) meemaken, zijn ze gematcht op genetische factoren, gedeelde omgevingsinvloeden, en uiteraard leeftijd en geslacht. Deze matching controleert zo voor deze mogelijke confounding variabelen die vaak niet gemeten of niet waarneembaar zijn, waardoor verschillen in uitkomsten met meer zekerheid kunnen worden toegeschreven aan de blootstelling (zoals slachtofferschap) zelf. Twee-eiige of dizygote (DZ) tweelingen kunnen ook meegenomen worden in het

CTCD. Hoewel twee-eiige tweelingen dezelfde omgeving delen, zijn ze genetisch niet identiek. Het vergelijken van discordante twee-eiige tweelingen geeft extra inzicht over de bron van confounding, maar biedt niet dezelfde mate van controle voor genetische confounding als bij MZ tweelingen.

Het CTCD is een robuuste methode voor het ontrafelen van causale effecten. Door gebruik te maken van dit design - in het bijzonder bij eeneiige tweelingen - verbetert de validiteit van de bevindingen en draagt het bij aan een beter begrip van de gevolgen van slachtofferschap.

Slachtofferschap en geestelijke gezondheid: De rol van familiale factoren

De relatie tussen slachtofferschap van misdrijven en geestelijke gezondheid, zoals depressie, angst en eenzaamheid, werd onderzocht in **hoofdstuk 3**, waarin analyses werden gedaan van gegevens van 19.867 individuen uit Nederlandse tweelingfamilies. Dit hoofdstuk laat zien dat slachtofferschap, met name van gewelddadige en seksuele misdrijven, sterk samenhangt met negatieve uitkomsten voor de geestelijke gezondheid. CTCD-analyses laten echter zien dat deze associaties mogelijk niet causaal zijn. Familiale factoren, waaronder genetische aanleg, dragen bij aan de associatie tussen slachtofferschap en psychische gevolgen. Deze bevinding benadrukt het belang van het betrekken van gedeelde genetische en omgevingsinvloeden bij het onderzoeken van de gevolgen van slachtofferschap en laat daarmee de waarde zien van genetisch informatieve designs die hiermee rekening houden. Door longitudinale gegevens op te nemen in de analyses ontdekte ik dat slachtoffers van seksuele en geweldsdelicten al verhoogde psychische gezondheidsproblemen vertoonden voordat ze slachtoffer werden, wat suggereert dat mensen met meer psychische gezondheidsproblemen en eenzaamheid een hoger risico lopen op dergelijk slachtofferschap.

De rol van sociale steun: Genetische invloeden en beschermende effecten

De **hoofdstukken 4 en 5** gingen in op de rol van sociale steun, waarbij zowel de genetische basis daarvoor als de rol van steun als beschermende factor tegen de

nadelige effecten van slachtofferschap van criminaliteit werden onderzocht. Met de gegevens van 8,019 volwassen tweelingen, rapporteert **hoofdstuk 4** een schatting van 37% voor de 'erfelijkheid' van sociale steun. Dat wil zeggen dat 37% van de variantie is toe te schrijven aan genetische factoren. Hiermee wordt het idee dat sociale steun uitsluitend een omgevingsfactor is, genuanceerd. Sociale steun blijkt beïnvloed te worden door zowel genetische als omgevingsfactoren. Hoewel de genetische invloed op sociale steun significant is, blijkt deze lager dan die van omgevingsfactoren.

In **Hoofdstuk 5** onderzocht ik hoe sociale steun algemene en geestelijke gezondheid beïnvloedt na slachtofferschap. Ik onderzocht zowel het hoofdeffect van sociale steun (d.w.z. de directe associatie met gezondheid) als ook een moderatie-effect (d.w.z. of sociale steun de negatieve impact van slachtofferschap op gezondheid buffert of vermindert). Een lagere mate van sociale steun bleek verband te houden met een slechtere algemene gezondheid en met depressie. Slachtofferschap was significant geassocieerd met slechtere gezondheid, waarbij slachtofferschap van een zedendelict de sterkste associatie liet zien. Naast deze hoofdeffecten had sociale steun ook een moderatie effect: meer sociale steun verminderde de negatieve effecten van slachtofferschap. De negatieve effecten van slachtofferschap van gewelddadige en seksuele misdrijven op de geestelijke gezondheid waren namelijk minder ernstig voor mensen met meer sociale steun dan voor mensen met minder steun. Dit suggereert dat sociale netwerken het trauma van slachtofferschap kunnen helpen reduceren door emotionele en praktische steun aan te bieden. De resultaten uit CTCD analyses waren in lijn met een causaal verband van sociale steun op depressie bij alle discordante tweelingvergelijkingen. Er was echter ook sprake van confounding door genetische en gedeelde omgevingsfactoren wanneer er werd gekeken naar het bufferende effect van sociale steun na slachtofferschap. Met andere woorden, genetische en omgevingsfactoren beïnvloeden de relatie tussen sociale steun en de gevolgen van slachtofferschap, waardoor deze relaties complex zijn.

Epigenetica en Biologische Veroudering: De Invloed van Levensgebeurtenissen en Slachtofferschap

Het laatste deel van het proefschrift is gewijd aan de impact van diverse negatieve levensgebeurtenissen (**hoofdstuk 6**) en specifiek slachtofferschap (**hoofdstuk 7**) op biologische veroudering zoals gemeten door epigenetische biomarkers.

In **hoofdstuk 6** werden verschillende epigenetische biomarkers onderzocht, namelijk Hannum, Horvath, PhenoAge, GrimAge en DunedinPACE. Deze zijn onderling matig gecorreleerd en bieden dus elk een unieke kijk op epigenetische gevolgen. De meerderheid van de deelnemers had meer dan één negatieve levensgebeurtenis meegemaakt, wat aangeeft dat, in plaats van dat er sprake is van geïsoleerde incidenten, cumulatieve levensstressoren veel voorkomen.

Het meemaken van een groter aantal negatieve levensgebeurtenissen hing samen met versnelde epigenetische veroudering, zoals gemeten door de GrimAge biomarker. Bij het onderzoeken van specifieke levensgebeurtenissen hingen financiële problemen en slachtofferschap van zedendelicten samen met een leeftijdsversnelling van respectievelijk ongeveer 1,6 jaar en 1,1 jaar. Financiële problemen hadden ook verband met een versneld tempo van veroudering, ongeveer 10 dagen per jaar, zoals gemeten door de DunedinPACE biomarker. Daarnaast werd ontslag in verband gebracht met een toename van 0,87 jaar in leeftijdsversnelling, volgens de GrimAge biomarker.

Na controle voor factoren waarvan bekend is dat ze geassocieerd zijn met epigenetische biomarkers, zoals BMI, rookgedrag en de proportie witte bloedcellen, bleef de associatie tussen het totale aantal levensgebeurtenissen en financiële problemen en epigenetische leeftijdsversnelling overeind voor de GrimAge biomarker. Het verband tussen het aantal meegemaakte levensgebeurtenissen en epigenetische leeftijdsversnelling was niet meer significant in de discordante tweelinganalyse, al wees het in dezelfde richting.

In **hoofdstuk 7** werd specifiek gekeken naar slachtofferschap van drie misdrijven, te weten zedendelicten, gewelddadige delicten en vermogensdelicten. Het recent meemaken van een zedendelict (d.w.z. minder dan 5 jaar geleden meegemaakt) hield verband met een epigenetische leeftijdsversnelling van respectievelijk 4, 7 en 4 jaar

volgens de Hannum, PhenoAge en GrimAge biomarkers, en een toename van het verouderingstempo met 60 dagen per jaar volgens de DunedinPACE biomarker. Wanneer er werd gekeken naar het ooit meemaken van een zedendelict (hetgeen betekent dat het slachtofferschap ook lang geleden kon zijn) was de invloed op epigenetische leeftijdsversnelling minder groot, namelijk met een toename van 1 jaar volgens de GrimAge biomarker en een toename van het tempo van ouder worden met 19 dagen per jaar zoals gemeten door de DunedinPACE biomarker.

Het verband tussen recent seksueel slachtofferschap en de Hannum en DunedinPACE biomarkers bleef significant, met slechts kleine afnames van de grootte van de effecten, na correctie voor mogelijke confounding factoren zoals BMI en roken. Ook het verband tussen het ooit meemaken van een zedendelict en de DunedinPACE biomarker bleef significant. Hoewel de eeneiige discordante tweelinganalyses niet significant waren, waren de effectgrootte slechts licht verminderd in vergelijking tot de uitkomsten in de volledige steekproef, wat suggereert dat het verband tussen seksueel slachtofferschap en epigenetische leeftijdsversnelling gedeeltelijk causaal kan zijn.

In dit proefschrift vond ik consistente verbanden tussen slachtofferschap van misdrijven en geestelijke gezondheid en biologische veroudering, die vooral duidelijk waren voor slachtoffers van seksuele misdrijven. Daarmee springt vooral slachtofferschap van zedendelicten eruit als een gebeurtenis die het leven negatief beïnvloedt: slachtoffers van zedenmisdrijven waren depressiever, angstiger, eenzamer en vertoonden ook een versnelde epigenetische veroudering.

Door gebruik te maken van het CTCD, laat dit onderzoek echter ook zien dat de verbanden tussen slachtofferschap en negatieve levensuitkomsten complex kunnen zijn, en dat lang niet alle correlationele verbanden als causale verbanden geïnterpreteerd mogen worden. Ik hoop dat mijn werk hiermee een basis voor nader onderzoek vormt om de mechanismen die ten grondslag liggen aan de gevolgen van slachtofferschap van misdrijven verder te ontrafelen.

Algemene discussie

Dit proefschrift draagt bij aan ons begrip van de complexe relatie tussen slachtofferschap van misdrijven, geestelijke gezondheid en biologische veroudering. Door gebruik te maken van het Co-Twin Control Design (CTCD) biedt dit proefschrift nieuwe inzichten in causaliteit versus correlatie, onderzoekt het meerdere typen slachtofferschap en verkent het de relatie met epigenetische veroudering. In deze discussie zal ik eerst ingaan op hoe deze bevindingen bijdragen aan de bestaande literatuur over slachtofferschap van misdrijven en gezondheid. Daarna zal ik ingaan op de sterke punten en limitaties van de methodologie, om een bredere context te bieden voor het interpreteren van de bevindingen.

Impact van slachtofferschap: de onzichtbare littekens

In eerder onderzoek naar slachtofferschap zijn de fysieke en psychologische gevolgen van slachtofferschap uitgebreid onderzocht. In dit proefschrift worden specifiek de psychologische en biologische gevolgen onderzocht, waarbij de nadruk ligt op problemen met de geestelijke gezondheid en epigenetische veroudering. Slachtoffers kunnen last hebben van gevolgen die niet direct duidelijk zijn voor de buitenwereld, zoals depressie, angst en epigenetische veranderingen. Deze “onzichtbare littekens” kunnen leiden tot aanzienlijke beperkingen in de kwaliteit van leven. In deze discussie zal ik bespreken hoe mijn bevindingen bijdragen aan de bestaande literatuur door in te gaan op een belangrijk thema, namelijk het onderscheid tussen causaliteit en correlatie.

Slachtofferschap, geestelijke gezondheid en de rol van familiaire factoren

De bevindingen in dit proefschrift bevestigen opnieuw dat slachtofferschap, in het bijzonder van gewelddadige en seksuele misdrijven, sterk samenhangt met geestelijke gezondheidsproblemen zoals depressie, angst, eenzaamheid en zelfgerapporteerde algemene gezondheid. De bevindingen van het CTCD bieden belangrijke nieuwe inzichten doordat deze suggereren dat er confounding is van familiale factoren, waaronder genetische aanleg, in de relatie tussen slachtofferschap en de geestelijke gezondheid. Deze resultaten brengen nuances aan in conclusies over de causale aard van dit verband. Dit proefschrift onderstreept daarmee het belang van het opnemen van

genetische aanleg en gedeelde omgevingsinvloeden in theoretische en statistische modellen van slachtofferschap en geestelijke gezondheid.

Dit proefschrift toont verder aan dat mensen met reeds bestaande psychische gezondheidsproblemen een grotere kans hebben om slachtoffer te worden van een misdrijf. Dit komt overeen met de criminologische theorie die stelt dat daders zich bij voorkeur richten op personen in meer kwetsbare situaties (bijv. Latalova, Kamaradova, & Prasko, 2014; Khalifeh et al.,2015, Monahan et al., 2017; Rossa-Roccor et al., 2020; Krahé & Berger 2017). Het benadrukt tevens het belang van het erkennen dat slachtofferschap disproportioneel diegenen treft die al kwetsbaar zijn voor negatieve gevolgen op het gebied van geestelijke gezondheid, wat hun kwetsbaarheid nog verder vergroot. Kwetsbaarheid voor slachtofferschap heeft dus niet alleen te maken met het feit dat je op het verkeerde moment op de verkeerde plek bent; het kan ook te maken hebben met dieperliggende, reeds bestaande psychische en familiaire factoren. Voor veel slachtoffers, is het slachtofferschap niet een op zichzelf staande ervaring. Een belangrijke bevinding in mijn proefschrift is dat slachtofferschap vaak voorkomt naast andere negatieve levensgebeurtenissen, d.w.z. slachtofferschap is niet altijd een geïsoleerde, willekeurige gebeurtenis, maar kan deel uitmaken van een breder patroon van blootstelling aan stress en trauma. Dit versterkt het idee dat genetische en omgevingsfactoren sommige mensen een groter risico kunnen geven op meerdere negatieve levensgebeurtenissen (Middeldorp et al., 2005).

Deze bevindingen maken duidelijk dat er een verschuiving nodig is in de manier waarop slachtofferhulp en misdaadpreventie worden aangepakt. Erkenning van het feit dat bepaalde mensen een groter risico lopen om slachtoffer te worden van een misdrijf, suggereert dat preventie- en interventieprogramma's zich ook moeten richten op het effectief voorkomen van slachtofferschap van risicogroepen, zoals mensen met psychische problemen. Aangezien genetische aanleg voor geestelijke gezondheidsproblemen de kans op slachtofferschap kan vergroten, kunnen familieleden die deze genetische factoren met elkaar delen ook een verhoogd risico lopen op zowel geestelijke gezondheidsproblemen als slachtofferschap. Kwetsbaarheid voor

slachtofferschap kan zich dus binnen families clusteren als gevolg van gedeelde genetische- en omgevingsinvloeden. Als we dit familierisico erkennen, is het belangrijk om familieleden te betrekken bij preventie en interventie. Door niet alleen individuen maar ook hun familieleden te ondersteunen, kunnen we de onderliggende kwetsbaarheden die bijdragen aan de cyclus van slachtofferschap en psychische problemen effectiever aanpakken. Bovendien lopen slachtoffers zelf een groot risico op geestelijke gezondheidsproblemen. Daarom moeten organisaties die hen ondersteunen in hun hulpverlening aandacht geven aan de aanpak van deze problemen, ongeacht of de geestelijke gezondheidsproblemen veroorzaakt zijn door het slachtofferschap of niet.

Sociale steun

Een belangrijke factor die de impact van slachtofferschap en deze reeds bestaande kwetsbaarheden kan bufferen, is sociale steun. In dit proefschrift vond ik dat een hogere mate van sociale steun geassocieerd was met betere mentale gezondheid en een verbeterde zelfgerapporteerde algemene gezondheid. Deze bevinding komt overeen met de bredere literatuur over sociale steun als beschermende factor tegen psychische stress (Harandi, Taghinasab, & Nayeri, 2017; Holt & Espelage, 2005; Scarpa, Haden, & Hurley, 2006). Sociale steun speelde ook een modererende rol en bufferde de negatieve effecten van slachtofferschap. De negatieve relaties tussen slachtofferschap en de geestelijke gezondheid, met name kijkend naar gewelds- en seksuele misdrijven, waren minder sterk voor mensen met meer sociale steun dan voor mensen met minder steun. Dit suggereert dat hulp, zoals aangeboden door slachtofferhulporganisaties en individuele sociale netwerken, het trauma van slachtofferschap kan helpen verzachten door emotionele en praktische hulpmiddelen aan te bieden.

Genetische invloeden op sociale steun, levensgebeurtenissen en slachtofferschap

In dit proefschrift ontdekte ik ook dat sociale steun zelf een deels erfelijke eigenschap is. Dit leidt tot een bredere heroverweging van wat we classificeren als een zogenaamde omgevingsfactor. Sociale steun vaak wordt gezien als een externe invloed, maar de bevindingen in dit proefschrift geven aan dat het ook wordt gevormd door onderliggende genetische factoren. Hiermee wordt de automatische classificatie van sociale steun—en soortgelijke factoren—als louter omgevingsfactoren in twijfel

getrokken. Eerder onderzoek heeft ook al aangetoond dat veel eigenschappen waarvan traditioneel gedacht wordt dat ze omgevingsfactoren zijn, significante genetische componenten kunnen hebben (Plomin & Bergeman, 1991; Vinkhuyzen et al., 2010).

Het concept dat zogenaamde omgevingsfactoren niet willekeurig zijn en beïnvloed worden door genetische factoren geldt ook voor negatieve levensgebeurtenissen, zoals slachtofferschap (Johnson et al., 2013). Middeldorp et al. (2005) vonden eerder dat genetische invloeden bijdragen aan het meemaken van bepaalde levensgebeurtenissen (specifiek voor ernstige ziekte van zichzelf of van een ander, overlijden van een geliefde, echtscheiding, ongeval en beroving). Hoewel de schattingen van de erfelijkheid voor deze levensgebeurtenissen niet extreem hoog zijn, verdienen ze toch aandacht. Ook Beaver et al. (2009) vonden dat genetische factoren tussen 40% en 45% van de variantie in slachtofferschap bij adolescenten verklaren, wat duidt op een aanzienlijke genetische invloed op de kans van slachtofferschap tijdens de adolescentie. De bevindingen benadrukken het belang van het heroverwegen van hoe we omgevingsrisicofactoren conceptualiseren in de context van slachtofferschap. In plaats van ze uitsluitend als externe factoren te beschouwen, is het belangrijk om de interactie tussen genetica en omgevingsinvloeden te erkennen.

Al met al benadrukt dit de noodzaak om genetisch geïnformeerde onderzoeksdesigns niet alleen te integreren in het onderzoek naar de gevolgen van slachtofferschap, maar ook in de sociale wetenschappen in het algemeen. Door rekening te houden met genetische invloeden kunnen onderzoekers causale relaties nauwkeuriger vaststellen en effectievere interventiestrategieën ontwikkelen die zowel de omgevings- als genetische factoren in acht nemen die bijdragen aan slachtofferschap en geestelijke gezondheidsproblemen.

Epigenetische Veroudering

Mijn proefschrift biedt nieuwe inzichten in de relatie tussen negatieve levensgebeurtenissen in het algemeen, en in het bijzonder slachtofferschap van misdrijven, en biologische veroudering. De bevindingen voor epigenetische markers, met name zoals gemeten door de GrimAge-biomarker, tonen aan dat het meemaken van

meerdere negatieve levensgebeurtenissen biologische sporen kan achterlaten die geassocieerd zijn met versnelde veroudering. Dit laat zien hoe belangrijk het is om rekening te houden met de opeenstapeling van stressfactoren in het leven, aangezien bepaalde mensen en groepen meer kans hebben om in de loop der tijd meerdere negatieve levensgebeurtenissen te ervaren. De literatuur toont consistent aan dat deze mensen niet alleen een hogere mate van stress ervaren, maar gedurende hun leven ook met verschillende stressfactoren te maken krijgen (Reiss et al., 2019; Nurius, LaValley & Kim, 2019). Dit vergroot de biologische belasting aanzienlijk, aangezien herhaalde blootstelling aan stress het verouderingsproces meer versnelt dan de meeste afzonderlijke gebeurtenissen.

Wanneer we kijken naar specifieke negatieve levensgebeurtenissen, benadrukken de bevindingen in dit proefschrift dat verschillende soorten stressoren, namelijk financiële problemen en seksuele misdrijven, geassocieerd zijn met versnelde epigenetische veroudering. Financiële problemen vertoonden een robuuste associatie met versnelde veroudering, zelfs na aanvullende correcties voor confounders, zoals BMI, roken en opleidingsniveau. Dit benadrukt de noodzaak van interventies gericht op het verlichten van economische lasten. Door te richten op het verminderen van financiële stress, zouden interventies kunnen bijdragen aan het verminderen van de versnelde veroudering die gepaard gaat met dergelijke stress.

Wat betreft slachtofferschap van seksuele misdrijven laten de bevindingen in dit proefschrift een genuanceerder beeld zien. In eerste instantie, toen ik het ooit meemaken van een seksueel misdrijf analyseerde, was mijn conclusie dat de associatie tussen slachtofferschap van seksuele misdrijven en biologische veroudering verdween na het controleren voor factoren zoals roken en variaties in BMI en het aantal witte bloedcellen. Dit suggereert dat leefstijlfactoren de relatie tussen slachtofferschap van seksuele misdrijven en epigenetische veroudering kan verklaren. Mensen met een ongezonde levensstijl lopen mogelijk een groter risico om zowel slachtoffer te worden als een versnelde epigenetische veroudering te vertonen. Risicogedrag dat samenhangt met een ongezonde leefstijl kan bijvoorbeeld leiden tot een blootstelling aan

omgevingen waar de kans op slachtofferschap groter is, terwijl het tegelijkertijd bijdraagt aan een snellere epigenetische veroudering door directe fysiologische effecten. Een andere mogelijkheid is dat deze leefstijlfactoren een rol spelen doordat ze veranderen als reactie op de ervaring van slachtofferschap van seksuele misdrijven. De stress van de gebeurtenis kan er bijvoorbeeld toe leiden dat slachtoffers meer gaan roken of ongezond(er) gaan eten, wat weer invloed kan hebben op de epigenetische veroudering. Daarnaast zou het zo kunnen zijn dat schommelingen in het aantal witte bloedcellen - een indicatie voor gezondheid en ontstekingsprocessen - de relatie tussen slachtofferschap van seksuele misdrijven en epigenetische veroudering mediëren. De ervaring van het slachtofferschap zou mogelijk kunnen leiden tot veranderingen in het aantal witte bloedcellen, waardoor ontstekingsreacties worden beïnvloed die cruciaal zijn bij epigenetische veroudering. Eerder onderzoek heeft aangetoond dat aandoeningen zoals angst en depressie, die vaak geassocieerd zijn met traumatische ervaringen, geassocieerd worden met verhoogde ontstekingsmarkers (Maes, 2011). Deze ontstekingsprocessen kunnen bijdragen aan epigenetische modificaties die epigenetische veroudering versnellen (Franceschi & Campisi, 2014).

In latere analyses breidde ik mijn steekproefgrootte uit om het ooit meemaken van seksuele misdrijven opnieuw te onderzoeken, en keek ik ook naar recent slachtofferschap van seksuele misdrijven (d.w.z. slachtofferschap in de afgelopen vijf jaar). In deze grotere steekproef was het ooit meemaken van een seksueel misdrijf significant geassocieerd met het tempo van veroudering volgens de DunedinPACE biomarker, zelfs na de aanvullende correcties. Wanneer we ons richtten op recent slachtofferschap, werd de invloed op epigenetische veroudering nog duidelijker. Het is mogelijk dat de associatie tussen slachtofferschap van een seksueel misdrijf en epigenetische veroudering—en het voortbestaan van deze associatie na correctie voor leefstijlfactoren en witte bloedcelwaarden—wordt gemedieerd door stressmechanismen. Deze hypothese vereist echter verder onderzoek.

Genetische en Omgevingsinvloeden op Levensgebeurtenissen, Slachtofferschap en Veroudering

Uit eeneiige discordante tweelinganalyses bleek dat de relatie tussen het aantal meegemaakte levensgebeurtenissen en epigenetische veroudering deels werd verklaard door genetische aanleg en gedeelde omgevingsfactoren. Het feit dat de associatie afnam bij controle voor familiale factoren impliceert dat mensen die dergelijke stressoren ervaren, onderliggende genetische of gedeelde omgevingskwetsbaarheden hebben die bijdragen aan zowel de kans op het meemaken van negatieve levensgebeurtenissen als aan versnelde epigenetische veroudering. Genetische factoren die gerelateerd zijn aan de stressrespons kunnen individuen een hoger risico op slachtofferschap geven. Verhoogde stressreactiviteit kan leiden tot gedrag dat als angstiger of kwetsbaarder wordt gezien. Daarnaast kunnen deze genetische factoren ook de vatbaarheid voor biologische veroudering vergroten, aangezien langdurige stress de cortisolniveaus verhoogt. Dit versnelt het verouderingsproces door toegenomen slijtage van het lichaam.

Als we kijken naar zedendelicten en epigenetische veroudering, bleek deze associatie niet significant na controle voor genetische en gedeelde omgevingsfactoren in het CTCD. Hoewel de effectgroottes vergelijkbaar bleven met die in de volledige steekproef, impliceert het gebrek aan statistische significantie dat we de versnelde epigenetische veroudering niet definitief kunnen toeschrijven aan slachtofferschap van een seksueel misdrijf, onafhankelijk van familiale factoren. Alhoewel de bevindingen hinten naar een directe biologische impact van seksuele slachtofferschap, is enige voorzichtigheid dus geboden bij het interpreteren van deze resultaten. Toekomstig onderzoek met grotere steekproeven en meer gedetailleerde metingen m.b.t. het delict, bijvoorbeeld metingen die verschillende typen seksuele delicten of vraagt naar de specifieke timing van het delict, zijn nodig om te bevestigen of slachtofferschap van seksuele misdrijven een direct gevolg heeft op epigenetische veroudering of dat de associatie voornamelijk wordt gedreven door gedeelde familiale factoren.

Evaluatie van de Methoden

In mijn inleiding heb ik aangegeven dat het begrijpen van de gevolgen van slachtofferschap een uitdaging is, vanwege de afhankelijkheid van observationele studies, die grote steekproeven vereisen met gedetailleerde informatie over zowel blootstellingen aan slachtofferschap als aan de gevolgen. Hier wil ik de methodologie en de keuze van epigenetische biomarkers als uitkomsten bespreken. Het CTCD biedt aanzienlijke voordelen, vooral omdat het controleert voor confounding variabelen die vaak niet gemeten of niet waarneembaar zijn, waardoor met meer zekerheid kan worden gesteld of het gevolg direct is toe te schrijven aan het slachtofferschap. Er moeten echter enkele methodologische overwegingen in acht worden genomen worden bij het interpreteren van de bevindingen.

Aannames van het CTCD

Het CTCD is waardevol omdat het controleert voor genetische en gedeelde omgevingsfactoren, die vaak een bron van confounding zijn in traditionele observationele studies. Door het vergelijken van tweelingen versterkt het CTCD de causale inferentie, doordat het rekening houdt met bestaande genetische en gedeelde omgevingsverschillen die zowel de blootstelling aan bijvoorbeeld slachtofferschap, als de uitkomst, zoals mentale gezondheid, beïnvloeden. Dit is met name belangrijk omdat het meemaken van een delict niet willekeurig is. Er zijn vooraf bestaande verschillen tussen degenen die slachtoffer worden en degenen die dat niet worden, waar traditionele observationele ontwerpen niet altijd voor kunnen controleren.

Een belangrijke aanname voor het maken van causale interpretaties op basis van het CTCD is de afwezigheid van confounding door unieke (omgevings)factoren die niet gemeten zijn. Hoewel het CTCD controleert voor genetische en gedeelde omgevingsinvloeden, veronderstelt het design dat unieke individuele ervaringen — zoals verschillende vriendschappen, werkomgevingen of stressvolle gebeurtenissen — geen invloed hebben op zowel de blootstelling (bijv. slachtofferschap) als de uitkomsten (bijv. mentale gezondheid of biologische veroudering). Onderzoek door Frisell et al. (2012) benadrukt dat het CTCD mogelijk gevoeliger is voor bias door niet-gedeelde confounders

dan wanneer er wordt gekeken naar slachtoffers en niet-slachtoffers die geen familie zijn van elkaar. Dit gebeurt met name als tweelingen meer verschillen in de unieke ervaringen, dan in de blootstelling waar naar gekeken wordt. Bias die door unieke confounders wordt geïntroduceerd kan leiden tot zowel over- als onderschatting van het causale effect. Als de unieke factoren bijvoorbeeld zowel de kans op slachtofferschap als mentale gezondheidsproblemen verhogen, kan de positieve associatie tussen slachtofferschap en mentale gezondheidsproblemen worden overschat. Omgekeerd, als ze in tegengestelde richtingen werken, kan het effect worden onderschat.

Hoewel het essentieel is om de mogelijkheid van bias door niet-gedeelde factoren te erkennen, wijzen eerdere onderzoeken erop dat de associatie tussen stressvolle levensgebeurtenissen en mentale gezondheidsuitkomsten grotendeels wordt beïnvloed door genetische factoren in plaats van niet-gedeelde omgevingsfactoren. Zo onderzochten Boardman et al. (2011) bijvoorbeeld de relatie tussen stressvolle levensgebeurtenissen en depressie door middel van een bivariate Cholesky-decompositie. Ze vonden dat ongeveer 55% van de correlatie tussen stressvolle levensgebeurtenissen en depressie te wijten was aan gemeenschappelijke genetische factoren die zowel stressvolle levensgebeurtenissen als depressie beïnvloeden. De resterende 45% werd toegeschreven aan gedeelde omgevingsinvloeden. Unieke omgevingsfactoren speelden geen significante rol in de associatie. Dit suggereert dat genetische factoren een substantiële bron zijn van de waargenomen relatie, en de invloed van niet-gedeelde omgevingsconfounders beperkt is.

Daarnaast observeerde ik in de analyses van dit proefschrift dat de positieve associatie tussen slachtofferschap en mentale gezondheidsuitkomsten werd verzwakt wanneer er rekening werd gehouden met genetische en gedeelde omgevingsfactoren wat suggereert dat confounding aanwezig is. Aangezien veel niet-gedeelde confounders — zoals persoonlijkheidseigenschappen of unieke stressoren — waarschijnlijk zowel het risico op slachtofferschap als mentale gezondheidsproblemen verhogen, zou de mogelijke bias die door deze factoren wordt geïntroduceerd ook eerder leiden tot een overschatting in plaats van een onderschatting van het causale effect. Dus zelfs als er

bias is door niet-gedeelde confounders, is de kans dat dit onze conclusies omkeert minimaal.

Het Spill-Over Effect

Een andere aanname van het CTCD is de afwezigheid van een zogenaamd 'spill-over' effect van de ene tweeling naar de ander —dat wil zeggen, de ervaringen van de ene tweeling heeft geen causale impact op de uitkomst van de andere tweeling (Smith et al., 2020). In de context van slachtofferschap geldt deze aanname mogelijk niet altijd vanwege de hechte emotionele banden en gedeelde ervaringen tussen tweelingen. Wanneer de ene tweeling bijvoorbeeld slachtofferschap ervaart, kan de andere tweeling indirect worden beïnvloed door emotionele stress, veranderingen in gedeelde omgevingen of wijzigingen in de gezinsdynamiek. Als een dergelijk spill-over effect aanwezig is, kan dit de verschillen binnen de tweeling paren in de bestudeerde uitkomstmaat verminderen en kan het leiden tot een onderschatting van het causale effect van slachtofferschap in het CTCD.

Om een mogelijk spill-over effect te onderzoeken, zijn longitudinale gegevens om veranderingen in de loop van de tijd te volgen essentieel. Door bijvoorbeeld te kijken naar de scores voor depressie of angst van beide tweelingen vóór en na het slachtofferschap, kunnen we bepalen of de uitkomsten van de tweelingbroer of -zus die geen slachtoffer is geweest wordt beïnvloed door de ervaring van hun co-tweeling. Vanwege de steekproefgrootte konden wij niet kijken naar de veranderingen in mentale gezondheid van de discordante tweelingen zowel voor als na het slachtofferschap. Echter, konden we wel de veranderingen in mentale gezondheid vóór en na slachtofferschap voor slachtoffers en al hun familieleden vergelijken. Hier vonden we geen bewijs van een spill-over effect van het slachtoffer naar hun familieleden. Zowel slachtoffers als hun familieleden vertoonden geen significante toename in mentale gezondheidsproblemen na het slachtofferschap. Dit suggereert dat er in alle waarschijnlijkheid geen sprake is van een spil-over effect binnen de analyses van dit proefschrift.

Meetfouten en Bias

Meetfouten kunnen ertoe leiden dat discordante paren onterecht als concordant (beide wel of niet slachtoffer) worden geclassificeerd, wat de associatie tussen slachtofferschap en de bekeken uitkomst kan verzwakken. Aangezien tweelingen vaak vergelijkbare omgevingen en ervaringen delen, kan zelfs een kleine meetfout een onevenredig groot effect hebben op de waargenomen associaties.

Gustavson et al. (2024) voerden een serie simulaties uit om bias in de onafhankelijke variabele door meetfouten te onderzoeken in modellen voor broers en zussen wanneer de waargenomen associatie causaal is. Zij tonen aan dat meetfouten kunnen leiden tot een onderschatting van de causale effecten. De studie benadrukte dat naarmate de betrouwbaarheid van de onafhankelijke variabele afneemt en de correlatie tussen de onafhankelijke variabele van broers en zussen toeneemt, de waargenomen associatie ten onrechte verzwakt wordt. Dit verhoogt het risico om ten onrechte te concluderen dat er sprake is van confounding door familiale factoren. Omdat de correlaties tussen eeneiige tweelingen over het algemeen hoger zijn dan die tussen broers en zussen en twee-eiige tweelingen, is dit probleem met name belangrijk in onderzoek kijkend naar eeneiige tweelingen. De bias die mogelijk door meetfouten ontstaan wordt versterkt wanneer de onafhankelijke variabele sterk is gecorreleerd binnen de eeneiige tweelingparen, maar onjuist is gemeten.

In onderzoek naar slachtofferschap zijn meetfouten in zelfgerapporteerde slachtofferschap inderdaad een zorg. Averdijk en Elffers (2012) vergeleken bijvoorbeeld zelfgerapporteerde slachtofferschap uit vragenlijsten met officiële politiegegevens. Ze vonden dat slechts 35% van het gerapporteerde slachtofferschap in de vragenlijst kon worden teruggevonden in de politiegegevens binnen de referentieperiode. Hoewel dit te verklaren is door het feit dat niet alle slachtoffers de delicten rapporteren bij de politie, ontdekten ze ook dat in 48% van de gevallen respondenten geen delict noemden in de vragenlijst die wel in de politiegegevens was geregistreerd. Deze discrepanties kunnen te wijten zijn aan misinterpretatie van vragen, fouten in politieverslagen, onderrapportage

in de vragenlijst of andere factoren, maar het geeft duidelijk aan dat sommige gebeurtenissen niet consistent worden gerapporteerd, herinnerd of geclassificeerd.

In de context van dit proefschrift is het onwaarschijnlijk dat meetfout alleen de niet-significante bevindingen in de meeste CTCD-analyses volledig kan verklaren. Hoewel een zekere mate van meetfout mogelijk heeft bijgedragen aan het verzwakken van de waargenomen associaties, suggereert de algehele consistentie in zelfrapportages van seksuele en gewelddadige slachtofferschap dat de meting relatief betrouwbaar was. In onze vragenlijsten rapporteerde slechts 2,43% van de deelnemers die in een eerdere vragenlijst aangaven slachtoffer van seksuele misdaad te zijn geweest, dit niet aan in een latere vragenlijst. Kijkend naar geweldsmisdrijven was dit slechts 3,20%. Het is mogelijk dat sommige delicten consistent verkeerd werden gerapporteerd — ofwel weggelaten of onjuist gerapporteerd in meerdere vragenlijsten. Maar, de lage discrepantie in de zelfrapportages voor seksuele en gewelddadige misdrijven suggereert dat een grote bias door meetfouten onwaarschijnlijk is voor deze delicten. Vermogensdelicten vertoonden een veel hogere inconsistentie (12,67%), wat kan zou kunnen leiden tot een impact van meetfouten in het CTCD. Echter, in de analyses in onze gehele steekproef vonden we ook geen significante associaties tussen het meemaken van een vermogensdelict en mentale gezondheidsproblemen of biologische veroudering. Het gebrek aan associaties kan mogelijk nog steeds door meetfouten worden beïnvloed, maar als dit zo is, dan is het geen probleem dat specifiek is voor het CTCD.

Toekomstige Richtingen voor Onderzoek

Gebaseerd op de bevindingen en beperkingen die in dit proefschrift zijn besproken, zijn er verschillende belangrijke onderzoekspaden voor toekomstig onderzoek die essentieel zijn voor het verdiepen van ons begrip van de complexe relatie tussen slachtofferschap en de gevolgen daarvan. Een belangrijke uitdaging in het onderzoek naar slachtofferschap is de meting van levensgebeurtenissen en blootstelling aan trauma. Gegevens over wanneer een delict plaatsvond, hoe vaak het gebeurde en de ernst van het delict zijn nodig om een genuanceerd beeld te krijgen van de impact van verschillende soorten slachtofferschap op mentale gezondheid, biologische veroudering

en andere uitkomsten te begrijpen. Toekomstig onderzoek moet zich richten op het verzamelen van meer gedetailleerde gegevens, zodat onderzoekers duidelijkere conclusies kunnen trekken over de timing, frequentie en impact van slachtofferschap van criminaliteit. Een manier om de dit te verbeteren, is door middel van koppeling van gegevens, waarbij zelfgerapporteerde delicten worden gekoppeld met officiële gegevens, zoals politie-, medische of juridische documenten. Deze aanpak zou een meer uitgebreide en valide dataset kunnen opleveren. Dit zou inzicht bieden in de discrepanties tussen zelfrapportages en officieel geregistreerde delicten, en zou onderzoekers helpen om patronen van onderrapportage of verkeerd rapporteren te identificeren. Gegevenskoppeling kan bovendien helpen om de nauwkeurigheid van de meting wanneer een delict heeft plaatsgevonden verbeteren.

Daarnaast moet toekomstig onderzoek kijken naar meer verschillende type delicten. Dit proefschrift heeft enkel gekeken naar vermogensdelicten, gewelddadige- en seksuele misdrijven, maar er is aanzienlijke variatie binnen deze categorieën dat verder onderzoek vraagt. Verschillende subtypes van vermogensdelicten (bijv. inbraak, diefstal, vandalisme), gewelddadige misdaden (bijv. mishandeling, beroving, huiselijk geweld) en seksuele slachtofferschap (bijv. intimidatie, aanranding, verkrachting) kunnen een verschillende psychologische en biologische impact hebben. Daarnaast is het ook van belang om nieuwe en opkomende vormen van slachtofferschap, zoals online intimidatie, identiteitsdiefstal of sextortion, te onderzoeken. Studies hebben al een associatie aangetoond tussen cybercriminaliteit slachtofferschap en nadelige mentale gezondheidsuitkomsten, waaronder verhoogde niveaus van angst, depressie en stress (Copp, Mumford, & Taylor, 2021; Gorissen et al., 2023; Hamby et al., 2020; Islam, Khanam, & Kabir, 2020). Deze studies tonen echter vaak correlaties aan en er kan dus sprake zijn van confounding door genetische en gedeelde omgevingsfactoren. Het is van essentieel belang dat toekomstig onderzoek mogelijke familiale en omgevingsconfounding in overweging neemt bij het onderzoeken van de impact van slachtofferschap va (cyber)criminaliteit.

Het is verder ook van belang dat er in toekomstig onderzoek wordt gekeken naar verschillende soorten gevolgen van slachtofferschap. Slachtofferschap heeft veel meer impact dan alleen op mentale en fysieke gezondheid — het kan ook andere “onzichtbare littekens” achterlaten bijvoorbeeld op het gebied van relaties, werk of inkomen. Door deze gevolgen te bestuderen, kan toekomstig onderzoek de volledige impact van slachtofferschap op individuen en de samenleving beter in kaart brengen. Een grondig begrip van deze gevolgen is cruciaal voor het ontwikkelen van effectieve preventieve interventies die niet alleen het welzijn van mensen bevorderen, maar ook de bredere maatschappelijke kosten kunnen verlagen.

Mijn bevindingen suggereren dat er sprake is van familiale confounding — de invloed van gedeelde genetische en omgevingsfactoren — wanneer we kijken naar de relaties tussen slachtofferschap en de gevolgen ervan. Dit benadrukt de noodzaak om in toekomstig onderzoek methoden toe te passen die rekening houden met deze confounding, zoals het CTCD of discordante broer- en zus design. Hoewel alleen eeneiige tweelingstudies volledig rekening houden met genetische confounding, zijn gegevens over eeneiige tweelingen mogelijk niet altijd beschikbaar. In dergelijke gevallen bieden andere op familie gebaseerde statistische modellen, zoals het discordante broer- en zus design, nog steeds waardevolle inzichten (D’Onofrio et al., 2013). Het vaker gebruik maken van dit soort modellen zal uiteindelijk een beter begrip geven van de werkelijke gevolgen van slachtofferschap.

Epigenetische Biomarkers en EWAS

Voortbouwend op de noodzaak van het gebruik van alternatieve methodes, zou toekomstig onderzoek ook moeten kijken naar een breder scala aan biologische variabelen om de effecten van slachtofferschap te onderzoeken. De epigenetische biomarkers —ook wel bekend als "epigenetische klokken"— die ik heb geanalyseerd om de biologische effecten van negatieve levensgebeurtenissen en specifiek slachtofferschap te onderzoeken, zijn representatief voor een verzameling van verschillende epigenetische markers. Epigenetische klokken zijn betrouwbare indicatoren van biologische veroudering. Ze kunnen worden afgeleid uit DNA-

methylatiegegevens van bloed, zijn gevalideerd in grootschalige datasets en bieden een praktische manier om biologische veranderingen te beoordelen. Deze biomarkers bieden waardevolle inzichten in de relatie tussen negatieve levensgebeurtenissen, zoals slachtofferschap, en biologische veroudering, en benadrukken zo een aspect van de lange termijn biologische gevolgen van trauma.

Één van de voordelen van het analyseren van epigenetische biomarkers is dat ze epigenetische informatie samenvatten in een kleinere set biologische markers, zodat een onderzoeker niet 400.000 of 800.000 variabelen hoeft te analyseren, maar slechts 5 of 6. Epigenetische biomarkers zijn dan ook een goede optie wanneer men wilt kijken naar een eigenschap of gebeurtenis met een relatief lage prevalentie, zoals zedendelicten. Dit betekent echter ook dat de epigenetische biomarkers mogelijk niet alle epigenetische veranderingen die met slachtofferschap samenhangen volledig vangen. Doordat ze zich richten op specifieke gebieden van het epigenoom die geassocieerd zijn met veroudering, kunnen ze epigenetische modificaties missen die verband houden met specifieke blootstellingen. Hoewel epigenetische klokken nuttig zijn voor het beoordelen van de algemene epigenetische veroudering, kunnen ze subtiele of unieke epigenetische veranderingen missen die een gevolg zijn van het slachtofferschap.

Om een completer begrip te krijgen van de epigenetische veranderingen die gepaard gaan met slachtofferschap, zou het nuttig zijn om een epigenoombrede associatie studie (EWAS) uit te voeren. Een EWAS onderzoekt de associatie tussen een variabele of ervaring en DNA-methylatieniveaus over het gehele genoom, waarbij honderden duizenden CpG-sites worden getest om epigenetische veranderingen te identificeren die met een specifieke variabele of ervaringen zijn geassocieerd.

De eerste studies die een EWAS hebben uitgevoerd hebben gekeken naar stressvolle ervaringen in de kindertijd en slachtofferschap tijdens de adolescentie. Zij vonden bewijs van gewijzigde DNA-methylatiepatronen bij mensen die slachtoffer waren geworden (Houtepen et al., 2018; Kandaswamy et al., 2021; Sumner et al., 2022). Toekomstig onderzoek met grote steekproeven kan profiteren van het uitvoeren van een EWAS om

specifieke loci – de locaties op chromosomen waar genen of genetische kenmerken zich bevinden – te identificeren die verband houden met slachtofferschap. Dit onderzoek zou ook kunnen helpen om te bepalen of deze veranderingen uniek zijn voor slachtofferschap of dat ze gedeeld worden met verschillende soorten stressoren.

Pooling van Gegevens en een Consortium voor Onderzoek naar Slachtofferschap en Levensgebeurtenissen

Om de besproken beperkingen aan te pakken en toekomstig onderzoek te bevorderen, is het essentieel om strategieën te ontwikkelen? voor het vergroten van steekproefgroottes, zoals het poolen van gegevens uit verschillende bronnen binnen Nederland en internationaal. Doordat slachtofferschap gelukkig relatief zeldzaam is, zijn grotere steekproeven nodig om robuuste analyses uit te voeren, vooral bij het onderzoeken van zeldzame gebeurtenissen zoals specifieke soorten delicten. Door gegevens te combineren kunnen we de statistische power vergroten, waardoor nauwkeurigere schattingen mogelijk zijn en de mogelijkheid om de effecten van meer zeldzamere gebeurtenissen te vinden. Natuurlijk brengt het bundelen van gegevens uit verschillende bronnen ook potentiële uitdagingen met zich mee. De betekenis en context van verschillende soorten delicten kunnen verschillen tussen datasets, afhankelijk van variaties in definities, meetinstrumenten of culturele contexten. Deze discrepanties kunnen de vergelijkbaarheid van gegevens en de validiteit van de conclusies die uit gecombineerde analyses worden getrokken beïnvloeden. Daarom zijn zorgvuldige harmonisatie van variabelen en consistente definities nodig bij het integreren van meerdere datasets.

Naast het poolen van gegevens zou het opzetten van een formeel *consortium voor onderzoek naar slachtofferschap en levensgebeurtenissen*, gericht op meta-analyses, waardevol zijn. Het oprichten van een consortium heeft eerder succesvol gewerkt in genetisch onderzoek en zou ons in staat stellen om resultaten uit verschillende studies te combineren om algemene trends en de effecten van slachtofferschap op geestelijke gezondheid, biologische veroudering en andere uitkomsten te identificeren. Door onze bevindingen te repliceren in diverse populaties en contexten kunnen we onze conclusies valideren en de bewijsbasis versterken. Bovendien zou een formeel

onderzoeksconsortium ons in staat stellen om een EWAS uit te voeren, waarmee we specifieke DNA-methylatie veranderingen die samenhangen met slachtofferschap kunnen identificeren. EWAS vereist grote steekproefgroottes omdat de effecten van slachtofferschap op DNA-methylatie waarschijnlijk subtiel zijn en verspreid over veel plekken in het genoom. Zonder voldoende statistische power kunnen kleinere studies deze associaties missen of ze ten onrechte detecteren door willekeurige variatie. Deze aanpak gaat verder dan het gebruik van epigenetische biomarkers en biedt een vollediger beeld van welke biologische sporen slachtofferschap achterlaat.

Uiteindelijk zou het bundelen van gegevens en het opzetten van een onderzoeksconsortium de interdisciplinaire samenwerking tussen onderzoekers uit verschillende velden — psychologie, genetica, epigenetica, sociologie en economie — bevorderen. Dit zou een uitgebreid inzicht geven in de impact van slachtofferschap op zowel individuen als de samenleving. Door middelen, expertise en gegevens te bundelen, zouden onderzoekers een breed scala aan gevolgen van slachtofferschap kunnen onderzoeken, zoals mentale gezondheid, biologische veroudering, financiële lasten, en sociale gevolgen. Zo een gezamenlijke inspanning zou essentieel kunnen zijn voor het sturen van toekomstig onderzoek, het ontwikkelen van beleid en het implementeren van interventies die gericht zijn op het voorkomen van slachtofferschap en het verlichten van de langdurige gevolgen.

Chapter 10.

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Chapter 11.

Supplements

Table S2.1. Correlations for the simulated exposure (y) and outcome (x) variables in twin pairs and cross-twin cross trait.

		Within Twins				Cross-Twin Cross-Trait				Difference scores
Scenario		**x1-x2**	**y1- y2**	**dx1-dx2**	**dy1-dy2**	**x1-y2**	**x2 - y1**	**dx1-dxy2**	**dx2 - dxy1**	**diff(y) - diff(x)**
A	MZ	0.45	0.48	0.45	0.48	0.33	0.33	0.33	0.32	0.18
	DZ	0.23	0.25	0.23	0.25	0.17	0.17	0.17	0.17	0.39
B	MZ	0.37	0.29	0.37	0.29	0.25	0.25	0.25	0.25	0.15
	DZ	0.19	0.15	0.18	0.14	0.12	0.12	0.12	0.12	0.37
C	MZ	0.35	0.25	0.35	0.25	0.23	0.23	0.21	0.23	0.12
	DZ	0.17	0.13	0.17	0.13	0.11	0.11	0.12	0.12	0.35
D	MZ	0.32	0.22	0.32	0.22	0.21	0.21	0.21	0.21	0.1
	DZ	0.16	0.11	0.16	0.1	0.1	0.1	0.11	0.12	0.33

A= no confounding, B = complete genetic confounding, C = complete shared environmental confounding, D = direct effect with genetic and shared environmental confounding. x = continuous exposure variable, dx = binary exposure variable, y = continuous outcome variable, dy = binary outcome variable.

Table S2.2. Results from the CTDT analyses conducted in R based on simulated data.

	y~x	95% CI			y~dx	95% CI			dy~x	95% CI			dy~dx	95% CI		
	(B)	LL	UL	N	(B)	LL	UL	N	(B)	LL	UL	N	(B)	LL	UL	N
Scenario A					**Linear regression**								**Logistic regression**			
Unrelated	0.35	0.341	0.359	50,000	0.553	0.535	0.571	50,000	0.563	0.544	0.583	50,000	0.857	0.821	0.893	50,000
					Fixed effects regression								**Conditional logistic regression**			
DZ twins	0.35	0.341	0.359	100,000	0.489	0.472	0.505	41,064*	0.702	0.674	0.729	40,606	0.959	0.907	1	40,606
MZ twins	0.35	0.341	0.359	100,000	0.420	0.341	0.359	33,410*	0.831	0.795	0.867	33,470	0.969	0.912	1.026	33,470
Scenario B					**Linear regression**								**Logistic regression**			
Unrelated	0.212	0.2036	0.221	50,000	0.337	0.319	0.354	50,000	0.349	0.331	0.368	50,000	0.563	0.527	0.598	50,000
					Fixed effects regression								**Conditional logistic regression**			
DZ twins	0.146	0.138	0.155	100,000	0.212	0.195	0.228	40,818*	0.312	0.288	0.336	40,236	0.447	0.403	0.491	40,236
MZ twins	0	-0.009	0.009	100,000	0.004	-0.009	0.009	33,300*	-0.001	-0.032	0.029	33,352	0	-0.051	0.053	33,352
Scenario C					**Linear regression**								**Logistic regression**			
Unrelated	0.035	0.027	0.044	50,000	0.043	0.026	0.061	50,000	0.069	0.052	0.087	50,000	0.095	0.059	0.129	50,000
					Fixed effects regression								**Conditional logistic regression**			
DZ twins	0	-0.009	0.009	100,000	0	-0.016	0.016	41,060*	-0.01	-0.035	0.011	40,250	-0.034	-0.077	0.009	40,250
MZ twins	0	-0.009	0.009	100,000	0.002	-0.009	0.009	33,206*	0.003	-0.027	0.033	33,388	0.002	-0.05	0.054	33,388
Scenario D					**Linear regression**								**Logistic regression**			
Unrelated	0.598	0.589	0.606	500,00	0.954	0.935	0.972	50,000	1.011	0.988	1.034	50,000	1.469	1.431	1.506	50,000
					Fixed effects regression								**Conditional logistic regression**			
DZ twins	0.494	0.485	0.502	100,000	0.697	0.679	0.714	14,034*	1.001	0.975	1.040	39,222	1.311	1.261	1.360	39,222
MZ twins	0.346	0.338	0.355	100,000	0.412	0.338	0.355	33,174*	0.831	0.793	0.868	30,649	0.946	0.891	1.002	30649

Note: * exact number not provided by software, thus needs to be calculated manually by calculating the discordant rate. y = continuous outcome variable, dy = binary outcome variable, x = continuous exposure variable, dx = binary exposure variable, B = regression coefficient, LL = lower limit of the confidence interval, UL = upper limit of the confidence interval.

Table S2.3. Results from the CTDT analyses conducted in STATA based on simulated data.

	y~x	95% CI			y~dx	95% CI			dy~x	95% CI			dy~dx	95% CI		
	(B)	LL	UL	N	(B)	LL	UL	N	(B)	LL	UL	N	(B)	LL	UL	N
Scenario A				**Linear regression**								**Logistic regression**				
Unrelated	0.35	0.341	0.359	50,000	0.553	0.535	0.571	50,000	0.563	0.544	0.583	50,000	0.857	0.821	0.893	50,000
				Fixed effects regression								**Conditional logistic regression**				
DZ twins	0.35	0.341	0.359	100,000	0.488	0.470	0.505	41,064*	0.702	0.674	0.729	40,606	0.954	0.907	1	40,606
MZ twins	0.35	0.341	0.359	100,000	0.420	0.405	0.436	33,410*	0.831	0.795	0.867	33,470	0.969	0.912	1.030	33,470
Scenario B				**Linear regression**								**Logistic regression**				
Unrelated	0.212	0.204	0.221	50,000	0.337	0.319	354	50,000	0.349	0.331	0.368	50,000	0.563	0.527	0.598	50,000
				Fixed effects regression								**Conditional logistic regression**				
DZ twins	0.146	0.138	0.155	100,000	0.212	0.195	0.228	40,818*	0.312	0.288	0.336	40,236	0.447	0.403	0.491	40,236
MZ twins	0	-0.008	0.008	100,000	0.004	-0.011	-0.019	33,300*	-0.001	-0.032	0.029	33,352	0.001	-0.051	0.053	33,352
Scenario C				**Linear regression**								**Logistic regression**				
Unrelated	0.035	0.027	0.044	50,000	0.043	0.026	0.061	50,000	0.069	0.052	0.087	50,000	0.095	0.059	0.129	50,000
				Fixed effects regression								**Conditional logistic regression**				
DZ twins	0	-0.009	0.009	100,000	0	-0.016	0.016	41,060*	-0.012	-0.035	0.011	40,250	-0.034	-0.0775	0.009	40,250
MZ twins	0	-0.009	0.009	100,000	0.002	-0.014	0.017	33,206*	0.003	-0.027	0.033	33,388	0.002	-0.05	0.055	33,388
Scenario D				**Linear regression**								**Logistic regression**				
Unrelated	0.598	0.589	0.601	50,000	0.954	0.935	0.972	50,000	1.01	0.988	1.034	50,000	1.469	1.431	1.506	50,000
				Fixed effects regression								**Conditional logistic regression**				
DZ twins	0.494	0.485	0.502	100,000	0.697	0.679	0.714	14,034*	1	0.975	1.040	39,222	1.310	1.261	1.360	39,222
MZ twins	0.347	0.338	0.355	100,000	0.412	0.397	0.428	33,174*	0.831	0.793	0.868	30,649	0.946	0.891	1.002	30,694

Note: * exact number not provided by software, thus needs to be calculated manually by calculating the discordant rate. y = continuous outcome variable, dy = binary outcome variable, x = continuous exposure variable, dx = binary exposure variable, B = regression coefficient, LL = lower limit of the confidence interval, UL = upper limit of the confidence interval.

Table S2.4. Results from the CTDT analyses conducted in SPSS based on simulated data.

	y~x	95% CI			y~dx	95% CI			dy~x	95% CI			dy~dx	95% CI		
	(B)	LL	UL	N	(B)	LL	UL	N	(B)	LL	UL	N	(B)	LL	UL	N
Scenario A					**Linear regression**								**Logistic regression**			
Unrelated	0.35	0.341	0.359	50,000	0.553	0.535	0.571	50,000	0.563	0.541	0.585	50,000	0.857	0.818	0.896	50,000
					Fixed effects regression								**Conditional logistic regression**			
DZ twins	0.35	0.344	0.356	100,000	0.489	0.469	0.508	41,064	0.702	0.536	0.729	40,606	0.954	0.810	1.001	40,606
MZ twins	0.35	0.344	0.356	100,000	0.42	0.398	0.442	33,410	0.831	0.796	0.866	33,470	0.969	0.912	1.026	33,470
Scenario B					**Linear regression**								**Logistic regression**			
Unrelated	0.212	0.204	0.221	50,000	0.337	0.32	0.354	50,000	0.349	0.331	0.367	50,000	0.563	0.528	0.598	50,000
					Fixed effects regression								**Conditional logistic regression**			
DZ twins	0.146	0.138	0.155	100,000	0.212	0.192	0.231	40,818	0.312	0.325	0.336	40,236	0.447	0.520	0.490	40,236
MZ twins	0	-0.008	0.008	100,000	0.004	-0.017	0.025	33,300	-0.001	-0.032	0.030	33,352	0.001	-0.052	0.054	33,352
Scenario C					**Linear regression**								**Logistic regression**			
Unrelated	0.035	0.027	0.044	50,000	0.043	0.026	0.061	50,000	0.07	0.052	0.088	50,000	0.095	0.060	0.130	50,000
					Fixed effects regression								**Conditional logistic regression**			
DZ twins	0	-0.009	0.009	100,000	0	-0.019	0.019	41,060	-0.012	0.046	0.012	40,250	-0.034	-0.077	0.009	40,250
MZ twins	0	-0.009	0.009	100,000	0.002	-0.02	0.023	33,206	0.003	-0.026	0.032	33,388	0.002	-0.051	0.055	33,388
Scenario D					**Linear regression**								**Logistic regression**			
Unrelated	0.597	0.589	0.606	50,000	0.954	0.935	0.972	50,000	1.001	0.977	1.025	50,000	1.469	1.432	1.506	50,000
					Fixed effects regression								**Conditional logistic regression**			
DZ twins	0.494	0.485	0.502	100,000	0.697	0.677	0.716	14,034	1.008	0.970	1.039	39,222	1.311	1.420	1.360	39,222
MZ twins	0.347	0.338	0.355	100,000	0.412	0.391	0.434	33,174	0.831	0.794	0.868	30,694	0.946	0.891	1.001	30,694

Note: 95% CI not provided by the software but is calculated using the standard error. y = continuous outcome variable, dy = binary outcome variable, x = continuous exposure variable, dx = binary exposure variable, B = regression coefficient, LL = lower limit of the confidence interval, UL = upper limit of the confidence interval.

Table S3.1. Descriptive statistics for sample characteristics, victimization rates and IRT scores of mental health variables, separate per survey.

	2000		**2002**		**2004**		**2009**	
	Mean (Min-Max)	**SD**	**Mean (Min-Max)**	**SD**	**Mean (Min-Max)**	**SD**	**Mean (Min-Max)**	**SD**
Loneliness					-0.021 (-0.73 - 2.54)	0.8	-0.036 (-0.61 - 2.67)	0.78
Anxiety	-0.05 (-2.07 - 3.74)	0.96	-0.04 (-2.19 - 3.28)	0.96				
Depression	-0.06 (-1.39 - 3.33)	0.93	-0.04 (-1.57 - 3.81)	0.926			-0.07 (-1.29 - 3.83)	0.88
Age	34.20 (25 - 90)	9.94	40.94 (25 - 85)	13.06	43.47 (25-80)	13.707	46.91 (25 - 97)	12.57
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Male	1,553	38.5	3,276	43.3	4,130	37.2	4,689	37.5
Female	2.485	61.5	4,294	56.7	6,962	62.8	7,829	62.5
Sexual Crime								
Not experienced	3,735	92.5	6,879	90.9	10,049	90.6	11,511	91.9
< 1 year ago	11	0.3	8	0.1	13	0.1	23	0.2
1-5 years ago	31	0.8	34	0.4	41	0.4	61	0.5
5+ years ago	201	5	422	5.6	631	5.7	768	6.1
Violent Crime								
Not experienced	3,728	92.3	6,843	90.4	10,096	91	11,628	92.9
< 1 year ago	39	1	51	0.7	57	0.5	63	0.5
1-5 years ago	69	1.7	161	2.1	155	1.4	144	1.2
5+ years ago	121	3	270	3.6	409	3.7	551	4.4
Property Crime								
Not experienced	2,984	73.9	5,107	67.5	7,709	69.5	8,251	65.9
< 1 year ago	265	6.6	553	7.3	507	4.6	525	4.2
1-5 years ago	395	9.8	774	10.2	977	8.8	1,061	8.5
5+ years ago	366	9.1	1,046	13.8	1,697	15.3	2,639	21.1

Table S3.2. Population analyses show the association between victimization and loneliness, anxiety and, depression, with victimization split by period of occurrence.

	Loneliness			Anxiety			Depression		
	B	**95% CI (LL - UL)**	**q**	**B**	**95% CI (LL - UL)**	**q**	**B**	**95% CI (LL - UL)**	**q**
Sexual Crime									
< 1 year ago	0.181	(-0.158 - 0.52)	0.438	0.148	(-0.267 - 0.564)	0.589	0.294	(-0.068 - 0.656)	0.176
1-5 years ago	0.140	(-0.056- 0.335)	0.278	0.422	(0.073 - 0.772)	0.039	0.320	(0.078 - 0.562)	0.023
5+ year ago	0.322	(0.260 - 0.384)	<0.001	0.386	(0.292 - 0.480)	<0.001	0.388	(0.315 - 0.461)	<0.001
Violent Crime									
< 1 year ago	0.214	(0.005 - 0.423)	0.176	0.058	(-0.195 - 0.312)	0.692	0.209	(0.001 - 0.417)	0.037
1-5 years ago	0.220	(0.106 - 0.333)	0.001	0.254	(0.104 - 0.404)	0.003	0.247	(0.105 - 0.389)	0.008
5+ year ago	0.201	(0.131 - 0.272)	<0.001	0.197	(0.09 - 0.305)	0.001	0.247	(0.168 - 0.326)	<0.001
Property Crime									
< 1 year ago	0.082	(0.018 - 0.145)	0.031	0.066	(-0.013 - 0.146)	0.149	0.029	(-0.041 - 0.099)	0.528
1-5 years ago	0.060	(0.015 - 0.105)	0.025	-0.032	(-0.103 - 0.038)	0.466	0.065	(0.013 - 0.118)	0.038
5+ year ago	0.024	(-0.007 - 0.056)	0.172	0.024	(-0.036 - 0.083)	0.511	0.040	(0.002 - 0.079)	0.096
Age (years)	0.001	(0 - 0.002)	0.171	-0.002	(-0.003 - -0.006)	0.097	-0.002	(-0.003 - -0.001)	0.001
Sex (ref = male)	0.181	(-0.158 - 0.52)	<0.001	0.261	(0.220 - 0.302)	0	0.370	(0.341 - 0.399)	<0.001

B = unstandardized regression coefficient, 95% CI = 95% confidence interval, LL = lower limit, UL = upper limit, q = FDR q-value.

Table S3.3. Population analyses showing the association between victimization and loneliness, anxiety and depression, per survey.

		Anxiety				Depression		
		B	**95% CI**		**q**	**B**	**95% CI**		**q**
Survey			LL	UL			LL	UL	
2000	Violent crime (ref = not experienced)	0.335	(0.195 - 0.475)		<0.001	0.339	(0.170 - 0.508)		<0.001
	Sexual crime (ref = not experienced)	0.264	(0.129 - 0.398)		<0.001	0.29	(0.119 - 0.462)		0.003
	Property crime (ref = not experienced)	0.019	(-0.049 - 0.088)		0.661	0.098	(0.021 - 0.175)		0.029
	Sex (ref = male)	0.286	(0.224 - 0.348)		<0.001	0.443	(0.372 - 0.515)		<0.001
	Age	-0.003	(-0.007 - 0.001)		0.163	-0.001	(-0.004 - 0.003)		0.698
		Anxiety				**Depression**			
		B	**95% CI**		**q**	**B**	**95% CI**		**q**
			LL	UL			LL	UL	
2002	Violent crime (ref = not experienced)	0.329	(0.227 - 0.430)		<0.001	0.324	(0.228 -0.420)		<0.001
	Sexual crime (ref = not experienced)	0.192	(0.096 - 0.288)		<0.001	0.163	(0.072 - 0.254)		0,002
	Property crime (ref = not experienced)	0.017	(-0.031 - 0.065)		0.592	0.049	(0.003 - 0.094)		0.078
	Sex (ref = male)	0.257	(0.213 - 0.301)		<0.001	0.479	(0.438 - 0.520)		<0.001
	Age	-0.001	(-0.003 - 0.001)		0.316	0	(-0.001 - 0.002)		0.836

Table S3.3. Continued

		Loneliness					
		B	95% CI		q		
			LL	UL			
2004	Violent crime (ref = not experienced)	0.231	(0.151 - 0.310)		<0.001		
	Sexual crime (ref = not experienced)	0.207	(0.128 - 0.285)		<0.001		
	Property crime (ref = not experienced)	0.021	(-0.015 - 0.057)		0.338		
	Sex (ref = male)	0.149	(0.118 - 0.180)		<0.001		
	Age	0.001	(0 - 0.002)		0.172		
		Loneliness				**Depression**	
		B	**95% CI**		**q**	**B**	**95% CI**		**q**
			LL	UL			LL	UL	
2009	Violent crime (ref = not experienced)	0.317	(0.249 - 0.385)		<0.001	0.364	(0.290 - 0.437)		<0.001
	Sexual crime (ref = not experienced)	0.211	(0.141 - 0.281)		<0.001	0.235	(0.159 - 0.310)		<0.001
	Property crime (ref = not experienced)	0.047	(0.017 - 0.077)		0.338	0.055	(0.020 - 0.089)		0.006
	Sex (ref = male)	0.146	(0.119 - 0.174)		<0.001	0.342	(0.310 - 0.375)		<0.001
	Age	0.001	(0 - 0.002)		0.172	-0.003	(-0.004 - -0.001)		<0.001

B = unstandardized regression coefficient, 95% CI = 95% confidence interval, LL = lower limit, UL = upper limit, q = FDR q-value.

Table S3.4. Results population analyses and analyses in the same-sex (SS) discordant twin pairs for loneliness, anxiety and depression, separately for violent crime, sexual crime and property crime.

	Violent Crimes				Sexual Crime				Property Crime			
	N	B	95% CI (LL - UL)	q	N	B	95% CI (LL - UL)	q	N	B	95% CI (LL - UL)	q
Loneliness												
Population analysis	16,378	0.294	(0.233 -0.355)	<0.001	16,378	0.203	(0.142 -0.263)	<0.001	16,378	0.04	(0.013 - 0.067)	0.01
SS DZ	79	0.0649	(-0.190 - 0.320)	0.664	82	0.082	(-0.160 - 0.325)	0.584	267	0.084	(-0.044 - 0.212)	0.32
MZ and SS DZ	164	0.078	(-0.052 -0.208)	0.336	236	0.056	(-0.079 - 0.191)	0.509	863	0.041	(-0.026 - 0.108)	0.33
MZ	18578	0.086	(-0.064 - 0.237)	0.36	154	0.041	(-0.121 - 0.204)	0.66	596	0.022	(-0.056 - 0.101)	0.64
Anxiety												
Population analysis	8,640	0.345	(0.250 - 0.440)	<0.001	8,640	0.204	(0.117 - 0.292)	<0.001	8,640	0.008	(-0.038 - 0.054)	0.75
SS DZ	39	0.226	(-0.218 - 0.670)	0.42	43	0.202	(-0.202 - 0.606)	0.422	459	-0.069	(-0.266 - 0.126)	0.57
MZ and SS DZ	127	0	(-0.211 - 0.211)	0.959	133	0.155	(-0.051 - 0.360)	0.235	489	-0.022	(-0.125 - 0.079)	0.69
MZ	88	-0.088	(-0.3246 - 0.148)	0.56	90	0.125	(-0.112 - 0.360	0.403	330	0	(-0.119 - 0.119)	0.96

Table S3.4. Continued

	Violent Crimes				Sexual Crime				Property Crime			
	N	**B**	**95% CI (LL - UL)**	**q**	**N**	**B**	**95% CI (LL - UL)**	**q**	**N**	**B**	**95% CI (LL - UL)**	**q**
Depression												
Population analysis	14,220	0.372	(0.302 - 0.441)	<0.001	14,220	0.238	(0.170 - 0.306)	<0.001	14,220	0.035	(0.003 - 0.067)	0.75
SS DZ	57	-0.018	(-0.373 - 0.336)	0.904	67	0.096	(-0.225 - 0.417)	0.621	250	0.156	(0.001 - 0.312)	0.109
MZ and SS DZ	225	0.115	(-0.382 - 0.268)	0.234	217	0.098	(-0.055 - 0.253)	0.321	778	0.053	(-0.024 - 0.129)	0.281
MZ	169	0.166	(0.002 - 0.332)	0.106	150	0.095	(-0.077 - 0.270)	0.333	538	0	(-0.083 - 0.090)	0.913

Note: N refers to the total sample in the population analyses and the total twin pairs in the discordant twin pairs analyses.

Table S3.5. Association between loneliness, anxiety and depression, and victimization, measured both pre- and post-victimization, comparison between victims and familial and non-familial non-victims.

		Prior Victimization				Post Victimization			
Loneliness		**N**	**B**	**95% (LL=UL)**	**q**	**N**	**B**	**95% (LL - UL)**	**q**
	Constant		0.581	(0.224 -0.939)	0.003		0.395	(0.042 - 0.749)	0.068
Sexual crime	Non-victim family member	23	-0.170	(-0.536 - 0.196)	0.481	23	-0.119	(-0.492 - 0.254)	0.638
(ref = victim)	Non-victim non-related	4110	-0.409	(-0.724 - -0.094)	0.032	4110	-0.294	(-0.601 - 0.014)	0.130
Violent crime	Non-victim family member	74	-0.216	(-0.488 - -0.056)	0.221	74	-0.08	(-0.34 - 0.179)	0.648
(ref = victim)	Non-victim non-related	4022	-0.296	(-0.5 - -0.092)	0.015	4022	-0.203	(-0.413 - 0.007)	0.128
Property crime	Non-victim family member	461	-0.094	(-0.191 - 0.003)	0.128	461	-0.09	(-0.180 - -0.001)	0.112
(ref = victim)	Non-victim non-related	3008	-0.059	(-0.127 - 0.01)	0.179	3008	-0.087	(-0.150 - -0.023)	0.023
Sex (ref = male)			0.127	(0.080 - 0.174)	<0.001		0.145	(0.100 - 0.190)	<0.001
Age			0.001	(-0.001 - 0.002)	0.717		$-3{,}46\times10^{-10}$	(-0.002 - 0.001)	0.740
Anxiety		**N**	**B**	**95% (LL=UL)**	**q**	**N**	**B**	**95% (LL=UL)**	**q**
	Constant		0.485	(-0.054 - 1.025)	0.154		0.463	(-0.115 - 1,041)	0.205
Sexual crime	Non-victim family member	16	-0.28	(-0.843 - 0.283)	0.452	16	-0.485	(-1,268 - 0.298)	0.357
(ref = victim)	Non-victim non-related	2104	-0.523	(-0.965 - -0.08)	0.056	2104	-0.558	(-1,053 - -0.062)	0.068
Violent crime	Non-victim family member	37	-0.023	(-0.404 - 0.359)	0.946	37	-0.078	(-0.524 - 0.368)	0.788
(ref = victim)	Non-victim non-related	2038	-0.133	(-0.413 - 0.146)	0.469	2038	-0.072	(-0.333 - 0.189)	0.674
Property crime	Non-victim family member	210	-0.094	(-0.244 - 0.055)	0.351	210	-0.103	(-0.264 - 0.057)	0.348
(ref = victim)	Non-victim non-related	1471	-0.09	(-0.193 - 0.013)	0.178	1471	-0.060	(-0.164 -0.043)	0.377
Sex (ref = male)			0.309	(0.226 - 0.392)	<0.001		0.315	(0.231 - 0.398)	<0.001
Age			-0.002	(-0.007 - 0.003)	0.490		-0.002	(-0.007 - 0.003)	0.604

Table S3.5. Continued

Depression		**N**	**B**	**95% (LL=UL)**	**q**	**N**	**B**	**95% (LL=UL)**	**q**
	Constant		0.350	(-0.087 - 0.787)	0.202		0.409	(0.019 - 0.800)	0.092
Sexual crime	Non-victim family member	18	-0.310	(-0.671 - 0.052)	0.186	18	-0.194	(-0.578 - 0.189)	0.448
(ref = victim)	Non-victim non-related	3706	-0.344	(-0.738 - 0.051)	0.179	3706	-0.295	(-0.638 - 0.049)	0.183
Violent crime	Non-victim family member	65	0.049	(-0.24 - 0.338)	0.781	65	-0.113	(-0.424 - 0.199)	0.602
(ref = victim)	Non-victim non-related	3610	-0.291	(-0.534 - -0.047)	0.052	3610	-0.317	(-0.587 - -0.048)	0.055
Property crime	Non-victim family member	445	-0.105	(-0.209 - -0.001)	0.128	445	-0.078	(-0.183 - 0.027)	0.257
(ref = victim)	Non-victim non-related	2662	-0.038	(-0.116 - 0.04)	0.457	2662	-0.046	(-0.126 - 0.035)	0.384
Sex (ref = male)			0.456	(0.399 - 0.514)	<0.001		0.357	(0.301 - 0.413)	<0.001
Age			-0.001	(-0.003 - 0.001)	0.592		-0.002	(-0.005 - 0)	0.062

Constant = mean score for victims, corrected for sex and age, B = unstandardized regression coefficient, 95% CI = 95% confidence interval, LL = lower limit, UL = upper limit, q = FDR q-value.

Table S6.1. Correlation Matrix for all Measured Life Events and Epigenetic Biomarkers.

	Life Events											
	Accident	**Violent Crime**	**Sexual Crime**	**Theft**	**Death of Partner**	**Death of Child**	**Illness Partner**	**Illness Child**	**Illness Self**	**End of Significant Relationship**	**Getting Fired**	**Financial Problems**
Accident	1	0.093	0.099	0.096	0.096	0.066	0.133	0.103	0.326	0.142	0.272	0.031
Violent Crime	0.093	1	0.288	0.322	-0.041	-0.066	0.108	0.098	0.116	0.030	0.349	0.239
Sexual Crime	0.099	0.288	1	0.053	-0.082	-0.103	0.068	0.085	0.179	0.186	0.283	0.079
Theft	0.096	0.322	0.053	1	0.137	0.091	0.140	0.024	0.114	0.074	0.178	0.102
Death of Partner	0.096	-0.041	-0.082	0.137	1	0.255	0.099	0.583	-0.051	0.186	0.213	0.193
Death of Child	0.066	-0.066	-0.103	0.091	0.255	1	0.536	0.274	0.157	0.065	0.271	0.472
Illness Partner	0.133	0.108	0.068	0.140	0.099	0.536	1	0.388	0.358	0.140	0.232	0.190
Illness Child	0.103	0.098	0.085	0.024	0.583	0.274	0.388	1	0.231	0.133	0.201	0.175
Illness Self	0.326	0.116	0.179	0.114	-0.051	0.157	0.358	0.231	1	0.146	0.254	0.120
End of Relationship	0.142	0.030	0.186	0.074	0.186	0.065	0.140	0.133	0.146	1	0.302	0.165
Getting Fired	0.272	0.349	0.283	0.178	0.213	0.271	0.232	0.201	0.254	0.302	1	0.324
Financial Problems	0.031	0.239	0.079	0.102	0.193	0.472	0.190	0.175	0.120	0.165	0.324	1

Table S6.1. Continued

	Epigenetic Biomarkers				
	AARH	**IEAA**	**AAPheno**	**AAGrim**	**DunedinPACE**
AARH	1	0.419	0.505	0.247	0.171
IEAA	0.419	1	0.378	0.075	-0.016
AAPheno	0.505	0.378	1	0.330	0.321
AAGrim	0.247	0.075	0.330	1	0.494
DunedinPACE	0.171	-0.016	0.321	0.494	1

Note: the life event matrix is based on tetrachoric correlations and the epigenetic biomarker matrix on spearman's correlation.

Table S6.2. Results of the GEE analyses looking at the association between the epigenetic biomarkers and the measured covariates.

	AARH		IEAA		AAPheno		AAGrim		DunedinPACE	
Covariates	**B**	**p**	**B**	**p**	**B**	**p**	**B**	**p**	**B**	**p**
Age	**-0,028**	**0,001**	-0,010	0,356	-0,031	0,011	**-0,031**	**1,30E-05**	**0,002**	**2,80E-15**
sex	**-1,381**	**4,82E-08**	-0,719	0,013	0,251	0,438	**-1,364**	**8,38E-13**	0,017	0,005
smoking	-0,130	0,263	-0,073	0,600	0,334	0,062	**2,426**	**1,75E-81**	**0,034**	**3,49E-24**
BMI	0,068	0,004	0,063	0,028	0,102	0,005	0,016	0,454	**0,005**	**9,99E-14**
White bloodcell count										
Monocytes	0,139	0,003	-0,056	0,307	0,215	0,003	-0,053	0,209	-0,002	0,276
Eosinophils	**0,214**	**2,42E-09**	0,067	0,095	**0,231**	**4,33E-04**	0,105	**4,19E-05**	9,50E-05	0,926
Neutrophils	**0,127**	**3,70E-36**	0,001	0,952	**0,236**	**2,30E-46**	**0,097**	**2,57E-26**	**0,004**	**4,13E-41**
Education	0,209	0,54	0,485	0,231	0,154	0,75	-1,268	4,68E-06	**-0,027**	**9,91E-04**

Table S6.3. Results of the GEE analyses looking at the association between life events and the measured covariates.

						White Bloodcell Count			
		Age	**Sex**	**Smoking**	**BMI**	**Monocytes**	**Eosinophils**	**Neutrophils**	**Education**
Accident	**B**	3.59E-04	-0.042	-0.005	-0.001	0.002	-0.004	0.002	-0.054
	p	0.685	0.099	0.700	0.855	0.662	0.266	0.144	0.170
Violent Crime	**B**	-3.26E-04	-0.022	0.019	0.003	0.003	0.005	-1.80E-04	0.044
	p	0.520	0.185	0.026	0.042	0.448	0.188	0.802	0.054
Sexual Crime	**B**	-0.001	**0.083**	0.029	0.000	-0.001	-0.001	-1.43E-04	-0.044
	p	0.218	**5.77E-12**	0.004	0.880	0.855	0.695	0.855	0.093
Theft	**B**	**0.003**	0.001	0.009	-0.002	-0.004	-0.004	-3.09E-04	**0.185**
	p	**0.002**	0.980	0.570	0.525	0.555	0.376	0.823	**9.34E-06**
Death of Partner	**B**	**0.002**	**0.018**	-0.004	-0.001	0.002	-0.001	2.22E-04	-0.013
	p	**6.83E-05**	**0.001**	0.346	0.290	0.154	0.435	0.603	0.254
Death of Child	**B**	**0.002**	0.003	-0.004	0.000	-0.003	0.002	-7.55E-05	0.013
	p	**6.79E-05**	0.709	0.469	0.661	0.077	0.394	0.878	0.384
Illness Partner	**B**	**0.005**	0.013	-0.005	0.003	0.001	0.003	1.60E-04	-0.018
	p	**3.45E-11**	0.453	0.634	0.225	0.829	0.390	0.877	0.521
Illness Child	**B**	**0.005**	0.041	0.007	0.002	-0.002	0.004	0.001	0.034
	p	**4.16E-10**	0.006	0.450	0.462	0.532	0.277	0.374	0.236
Illness Self	**B**	**0.004**	-0.010	-0.016	0.005	0.002	0.001	0.001	-0.021
	p	**1.01E-05**	0.696	0.242	0.161	0.773	0.813	0.578	0.591
Getting Fired	**B**	**0.004**	-0.074	0.037	-0.004	-0.007	0.004	0.002	-0.038
	p	**4.54E-06**	0.003	0.006	0.146	0.135	0.429	0.142	0.288
Financial Problems	**B**	0.002	-0.018	0.031	0.003	0.005	1.96E-04	0.002	-0.009
	p	0.014	0.333	0.004	0.291	0.180	0.931	0.080	0.731

Table S6.3. Continued									
End of Significant Relationship	**B**	**0.003**	**0.063**	0.034	-0.004	0.002	0.005	0.003	-0.038
	p	**1.29E-04**	**0.002**	0.010	0.123	0.619	0.225	0.004	0.265

Table S6.4. Results from the GEE Analyses Investigating the Associations Between Epigenetic Aging and All Negative Life Events Estimated both Simultaneously and Separately, adjusted for Age, Sex, BMI, smoking, white blood cell count, Educational Attainment, array row number and bisulfite plate.

	Hannum			IEAA			PhenoAge			GrimAge			DunedinPACE		
Life events	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**
Any Life event	-0.036	0.066	0.075	0.128	0.066	0.035	0.133	0.155	0.045	**0.302**	**2.20E-05**	**0.081**	0.005	0.008	0.135
Life Events Considered Simultaneously															
	Hannum			**IEAA**			**PhenoAge**			**GrimAge**			**DunedinPACE**		
Life events	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**
Accident	0.127	0.554		0.102	0.650		0.146	0.649		0.175	0.317		3.80E-03	0.480	
Violent Crime	0.208	0.686		0.563	0.181		-0.093	0.881		0.065	0.846		-0.016	0.084	
Sexual Crime	-0.527	0.149		-0.655	0.045		-0.932	0.040		0.192	0.504		0.006	0.481	
Theft	-0.169	0.413		0.025	0.905		0.135	0.637		-0.144	0.374		-0.004	0.418	
Death of Partner	0.561	0.306		0.640	0.282		0.973	0.321		0.912	0.099		0.020	0.146	
Death of Child	-0.573	0.542		1.437	0.079		1.309	0.262		0.833	0.247		0.006	0.683	
Illness of Partner	-0.350	0.260	0.088	-0.702	0.058	0.045	-0.215	0.642	0.206	0.179	0.476	0.448	0.004	0.601	0.392
Illness of Child	-0.259	0.402		-0.122	0.716		-0.536	0.251		-0.433	0.110		-0.004	0.647	
Illness Self	0.085	0.697		0.170	0.486		0.492	0.107		0.249	0.180		0.008	0.116	
Job loss	0.338	0.194		0.220	0.414		0.280	0.406		0.254	0.232		0.008	0.224	
Financial Problems	-0.136	0.648		0.260	0.420		0.263	0.509		0.807	0.004		0.017	0.034	
End of Relationship	0.011	0.972		-0.072	0.852		-0.523	0.246		0.093	0.715		-0.008	0.277	

Table S6.4. Continued

Life Events Considered Separately															
	Hannum			IEAA			PhenoAge			GrimAge			DunedinPACE		
Life events	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**
Accident	0.114	0.590	0.084	0.134	0.550	0.039	0.223	0.477	0.199	0.274	0.110	0.437	0.006	0.265	0.382
Violent Crime	0.093	0.850	0.084	0.514	0.213	0.040	-0.187	0.755	0.199	0.114	0.722	0.436	-0.016	0.077	0.383
Sexual Crime	-0.500	0.166	0.085	-0.593	0.069	0.040	-0.872	0.054	0.201	0.327	0.259	0.437	0.007	0.356	0.382
Theft	-0.156	0.430	0.084	0.059	0.775	0.039	0.140	0.616	0.199	-0.077	0.635	0.436	-0.004	0.386	0.382
Death of Partner	0.477	0.370	0.084	0.582	0.332	0.039	0.790	0.406	0.199	0.771	0.134	0.437	0.019	0.185	0.382
Death of Child	-0.670	0.469	0.084	1.249	0.129	0.039	1.263	0.281	0.199	1.095	0.134	0.437	0.009	0.559	0.382
Illness of Partner	-0.408	0.172	0.085	-0.598	0.097	0.041	-0.140	0.758	0.199	0.295	0.236	0.437	0.006	0.404	0.382
Illness of Child	-0.247	0.413	0.084	-0.112	0.735	0.039	-0.463	0.313	0.199	-0.265	0.329	0.436	-0.001	0.926	0.382
Illness Self	0.037	0.862	0.084	0.137	0.566	0.039	0.453	0.133	0.200	0.330	0.072	0.438	0.009	0.069	0.384
Job loss	0.285	0.265	0.084	0.185	0.492	0.039	0.249	0.453	0.199	0.352	0.097	0.437	0.010	0.120	0.383
Financial Problems	-0.150	0.602	0.084	0.281	0.377	0.039	0.247	0.528	0.199	**0.949**	**9.23E-04**	**0.443**	0.018	0.019	0.386
End of Relationship	-0.025	0.931	0.084	0.084	0.824	0.039	-0.377	0.383	0.200	0.295	0.245	0.436	-0.005	0.488	0.382

Note: Bold coefficients are significant (p<.002). B = unstandardized regression coefficient, R^2 = the proportion of variance in epigenetic age acceleration explained by the model, which includes the number of negative life events and other covariates. AARH = Age Acceleration Residual Hannum, IEAA = Intrinsic Epigenetic Age Acceleration, AAPheno = Age Acceleration PhenoAge, AAGrim = Age Acceleration Grim Age, DunedinPACE = Dunedin Pace of Ageing.

Table S6.5. Number of Discordant and Concordant Complete MZ twin pairs (N_{total}= 411 pairs) for Number of Life Events.

	Discordant		Concordant Not Experienced		Concordant Experienced	
	N	**%**	**N**	**%**	**N**	**%**
MZ twins	263	63.99%	78	18.98%	70	17.03%

Table S6.6. Results of the within-pair analyses of monozygotic (MZ) twins discordant for the number of life events.

	Hannum			IEAA			PhenoAge			GrimAge			DunedinPACE		
	B	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**	**B**	**p**	**R2**
Model 1	-0.086	0.440	0.141	0.147	0.141	0.120	-0.065	0.693	0.212	0.097	0.352	0.121	9.67E-04	0.709	0.202
Model 2	-0.029	0.789	0.279	0.147	0.140	0.165	-0.033	0.830	0.313	0.080	0.394	0.309	2.37E-03	0.302	0.403
Model 3	-0.170	0.215	0.271	0.031	0.779	0.290	-0.061	0.759	0.313	0.024	0.825	0.366	-0.001	0.741	0.437

Note: model 1 corrects for technical covariates, model 2 additionally corrects for lifestyle factors and white blood cell counts (except for the Hannum biomarker), model 3 additionally adjust for Educational Attainment. B = unstandardized regression coefficient, R^2 = the within R^2 from the fixed effects regression models used in the discordant twin analyses. It represents the proportion of variance in epigenetic age acceleration explained by the differences in the number of negative life events within monozygotic twin pairs, along with other covariates included in the model. AARH = Age Acceleration Residual Hannum, IEAA = Intrinsic Epigenetic Age Acceleration, AAPheno = Age Acceleration PhenoAge, AAGrim = Age Acceleration Grim Age, DunedinPACE = Dunedin Pace of Ageing.

Supplementary Methods S7.1

Participants and samples

The participants in this study participated in the Netherlands Twin Register (NTR) biobank project (Willemsen et al., 2010). DNA methylation was measured in venous whole blood samples, which were drawn in the morning after an overnight fast, and multiple EDTA and other tubes were collected for isolation of DNA and assessment of haematological profiles. The blood sample collection procedures of the Netherlands Twin Register were described in detail previously https://www.nature.com/articles/ncomms11115 (Willemsen et al., 2010). DNA methylation data were generated in multiple batches. The first, and largest set, was measured on Illumina 450k arrays at the Erasmus MC Human Genomics Facility (HuGe-F) in collaboration with the BBMIR-NL BIOS Consortium in 2014, as described in van Dongen et al. 2016. Of the 3089 samples with Illumina 450k array data that passed quality control (van Dongen et al. 2016), 3081 were included in the current ("freeze 2024") DNA methylation dataset; samples from participants who retracted their permission for data use were excluded. Between 2021 and 2023, good quality DNA methylation profiles were obtained with Illumina EPICv1 arrays for 915 additional blood samples at the Avera McKennan Hospital, including 574 samples from the NTR biobank project, and 341 samples collected in the mid-1990s as part of a study on asthma (van Asselt et al., 2023), bringing the total number of whole blood samples with Illumina 450k or EPIC array DNA methylation profiles to 3996. In the current study focusing on victimization, we only included DNA methylation profiles of samples from the NTR biobank project (N=3655), because survey information on victimization was limited for individuals for whom only a blood sample from the asthma study in the mid-1990s was available.

DNA methylation

Detailed information on DNA extraction, DNA methylation profiling and quality control has been provided previously for the Illumina 450k array data in van Dongen et al. (2016). The Illumina EPICv1 array data were generated in two batches between 2021 and 2023 at the Avera McKennan Hospital. The first batch included 341 samples collected in the mid-

1990s as part of the asthma study and 232 blood samples collected from the same individuals who also participated in the NTR biobank project (573 in total, after QC). Detailed information on DNA extraction, DNA methylation profiling and quality control has been described previously for these 573 samples in van Asselt et al. (2023). The second Illumina EPICv1 blood sample batch included 342 NTR biobank blood samples from twins for whom no DNA methylation profiles had been measured

previously. In total, 344 samples from 172 twin pairs were assessed for genome-wide methylation, of which 342 samples passed quality control. DNA methylation was assessed with the Infinium MethylationEPIC BeadChip Kit (Illumina, San Diego, CA, USA) by the Avera McKennan Hospital as previously described (van Asselt et al., 2023). For all samples (450k and EPIC), quality control (QC) and normalization were performed using the same pipeline developed by the Biobank-based Integrative Omics Study (BIOS) consortium (Sinke, Van Iterson, Cats, Slieker & Heijmans, 2019), which includes sample quality control using the R package MethylAid (van Iterson et al., 2014), probe filtering and functional normalization as implemented in the R package DNAmArray, sample sex checks (DNAmArray) and sample identity checks based on genotype data (omicsPrint) (van Iterson et al., 2018). Functional normalization was performed based on the dataset-specific optimal number of control probe PCs (four PCs for the 450k array data, four PCs for the first EPICv1 array batch, and two PCs for the second EPICv1 array batch).

Cell counts

We calculated cellular proportions for all samples using the IDOL (Identifying Optimal Libraries) whole blood reference library, which is specifically optimized for estimating cellular composition in whole blood samples (Salas et al., 2018; Wiencke et al., 2016)

Epigenetic Age Biomarkers

DNAmAge and DNAmAge acceleration (that is, the residuals from the regression of DNAmAge on chronological age) were calculated with the R package dnaMethyAge for five epigenetic age biomarkers (Horvath, Hannum, Levine PCPhenoAge, PCGrimAGe, and DunedinPACE). Two approaches to combine the different datasets were compared. Approach 1 involved pooling at the level of DNA methylation beta-values (maintaining

only the common set of probes present on 450k and EPICv1 arrays and that survived QC in all datasets), followed by simultaneous estimation of DNAmAge and DNAmAge acceleration). Approach 2 involved separate estimation of DNAmAge and DNAmAge acceleration within each dataset followed by subsequent pooling of the DNAmAge and DNAmAge acceleration data. The accuracy of chronological age estimation (based on the Horvath epigenetic clock), as assessed by the RMSD and MAD, and distribution of all measures of DNAmAge acceleration was compared across datasets. Based on this comparison, it was concluded that approach 2 is favorable. While both approaches yielded similar strong correlations between chronological age and Horvath DNAmAge (r>= 0.97, Supplementary Table S.7.1, Supplementary Figure S.7.1), and approach 1 yielded slightly better (lower) RMSD and MAD, approach 1 led to a systematic bias, with samples measured on EPIC arrays having a lower estimated DNAmAge compared to 450k arrays (Supplementary Figure S7.2). This bias was not present with approach 2 (Supplementary Figure S7.3).

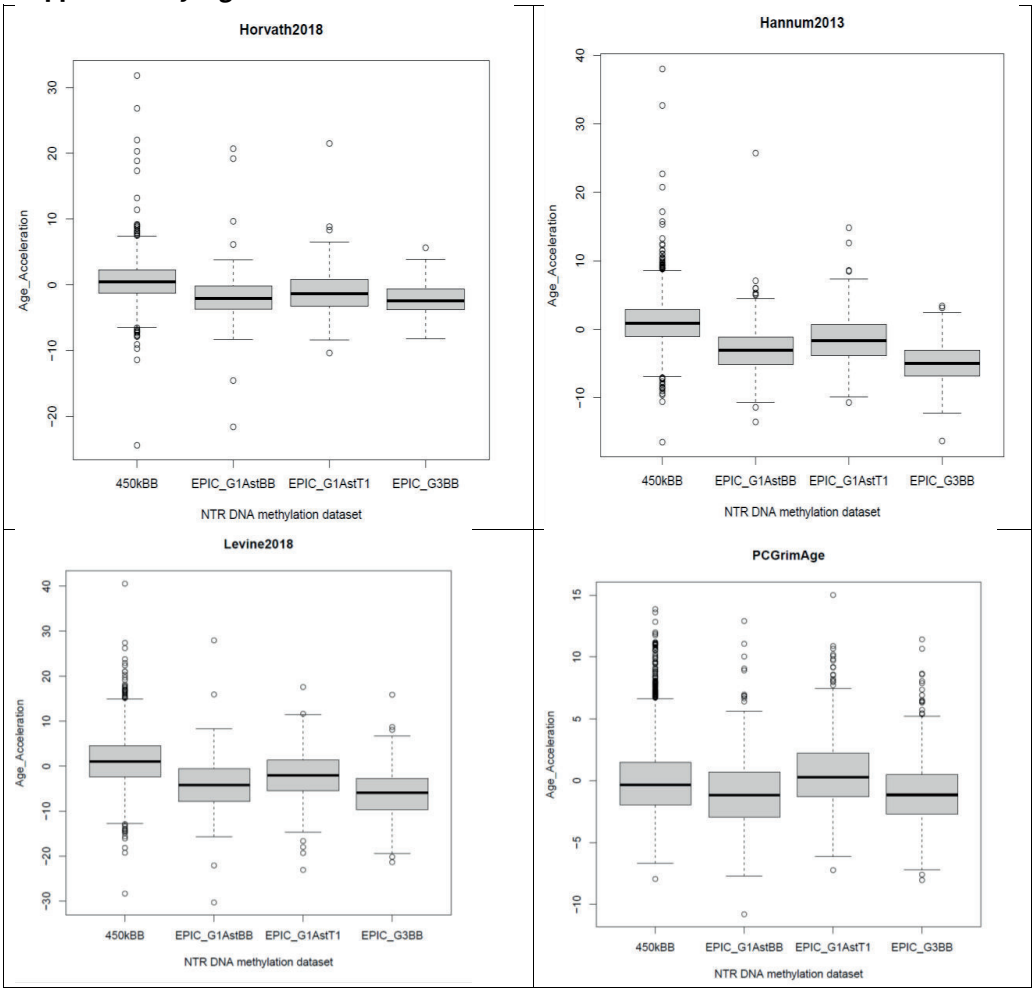
Supplementary Figure S7.2 (continues next page) shows the distribution of the DNAmAge acceleration residuals for 5 epigenetic age biomarkers in each of the 4 NTR blood DNA methylation datasets, where DNAmAge and DNAmAge acceleration residuals were calculated simultaneously on a single pooled DNA methylation beta-value dataset (N=3996 samples) including only probes that pass QC in all 4 datasets. Note that variation in estimated epigenetic age by chronological age clocks is more likely related to technical error (especially for Horvath), whereas variation in biological age clocks ("second" and "third" generation clocks) will include both measurement error and true biological variation. Therefore, it is more difficult to compare median levels of second and third generation age clocks across different dataset that differ in e.g. chronological age distribution (as is the case here, see final boxplot).

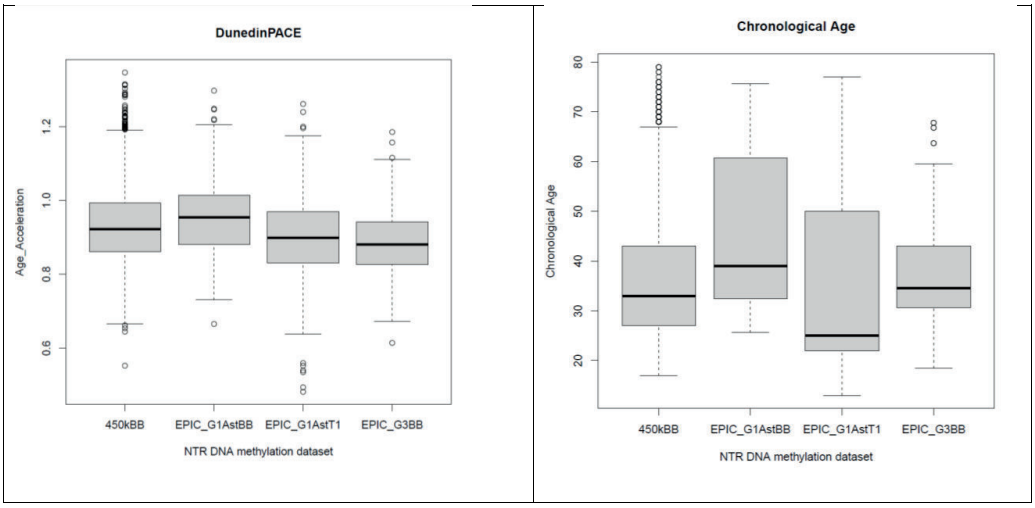
Supplementary Table S7.1 – Overview of NTR Blood DNA methylation datasets (450k and EPICv1 arrays), and accuracy of the Horvath epigenetic clock in individual and merged datasets .

Array	DNA source	Dataset	N blood samples	*r* DNAmAge-chronological age	RMSD	MAD
450k	Blood NTR biobank	450k_2014_BIOS_NTR_BloodBiobank - FREEZE 2024 https://www.nature.com/articles/ncomms11115	3081*	0.975	3.18	2.39
EPICv1	Blood NTR biobank	EPIC_AVERA_2022_GROUP3_ BloodBiobank (not previously published)	342	0.973	3.18	2.59
EPICv1	Blood NTR biobank	EPIC_AVERA_2022_GROUP1_Asthma - Timepoint 2 https://pubmed.ncbi.nlm.nih.gov/37834090/	232	0.969	3.93	2.34
EPICv1	Blood Asthma Project (Henk Los et al)	EPIC_AVERA_2022_GROUP1_Asthma - Timepoint 1 https://pubmed.ncbi.nlm.nih.gov/37834090/	341	0.981	3.09	2.34
450k+ EPICv1	Blood NTR biobank	Combined_Before_allBiobankSamples (Approach 1)	3655	0.972	3.08	2.29
450k+ EPICv1	Blood NTR biobank+ Blood Los Asthma Project	Combined_Before_allBloodSamples (Approach 1)	3996	0.973	3.08	2.30
450k+ EPICv1	Blood NTR biobank+ Blood Los Asthma Project	Combined_After_allBloodSamples (Approach 2)**	3996	0.972	3.22	2.42

The table summarizes characteristics and performance of the HorvathS2018 epigenetic clock in four subsets of the NTR Illumina DNA methylation datasets (which differ by array used; 450k versus EPICv2, and by blood sample collection moment; NTR biobank versus asthma project). The bottom three rows show 3 distinct versions of the merged dataset. RMSD=Root-mean-square-deviation, MAD= Mean absolute deviation. *freeze 2024 – people who retracted permission for data use have been excluded. The original dataset described in van Dongen et al 2016 included 3089 samples after QC. **Dataset utilized in the current project described in Chapter 7 of this thesis.

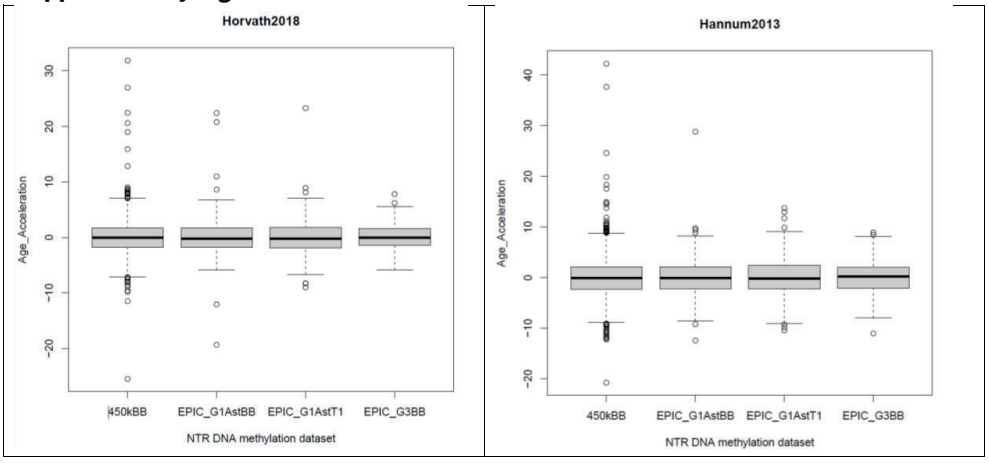
Supplementary Figure S.7.2

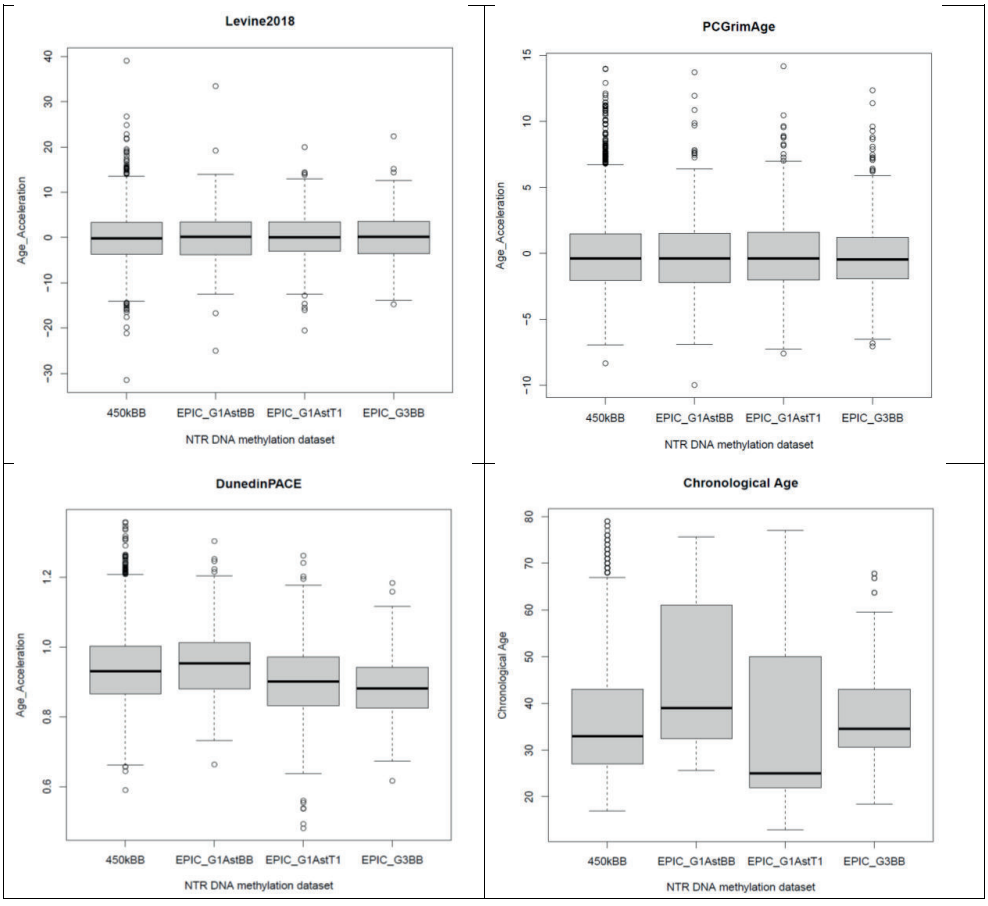




Supplementary Figure S.7.3 (continues next page) Distribution of the DNAmAge acceleration residuals for 5 epigenetic age biomarkers in each of the 4 NTR blood DNA methylation datasets, where DNAmAge and DNAmAge acceleration residuals were calculated in each dataset separately using the dataset-specific set of probes that pass QC. Next, the estimated DNAmAges and Age acceleration were pooled in one overall dataset N=3,996. This approach avoids that age acceleration residuals will capture technical variation between datasets.

Supplementary Figure S7.3




Levine2018
Age_Acceleration
450kBB
EPIC_G1AstBB
EPIC_G1AstT1
EPIC_G3BB
NTR DNA methylation dataset
PCGrimAge
Age_Acceleration
450kBB
EPIC_G1AstBB
EPIC_G1AstT1
EPIC_G3BB
NTR DNA methylation dataset
DunedinPACE
Age_Acceleration
450kBB
EPIC_G1AstBB
EPIC_G1AstT1
EPIC_G3BB
NTR DNA methylation dataset
Chronological Age
Chronological Age
450kBB
EPIC_G1AstBB
EPIC_G1AstT1
EPIC_G3BB
NTR DNA methylation dataset

List of Publications

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Gonggrijp, M. A., van de Weijer, G. A., Bijleveld, C. J. H., Boomsma, I. D., & van Dongen, J. (2024). Negative Life Events and Epigenetic Ageing: a Study in the Netherlands Twin Register. *Behavior Genetics*, 1-16.

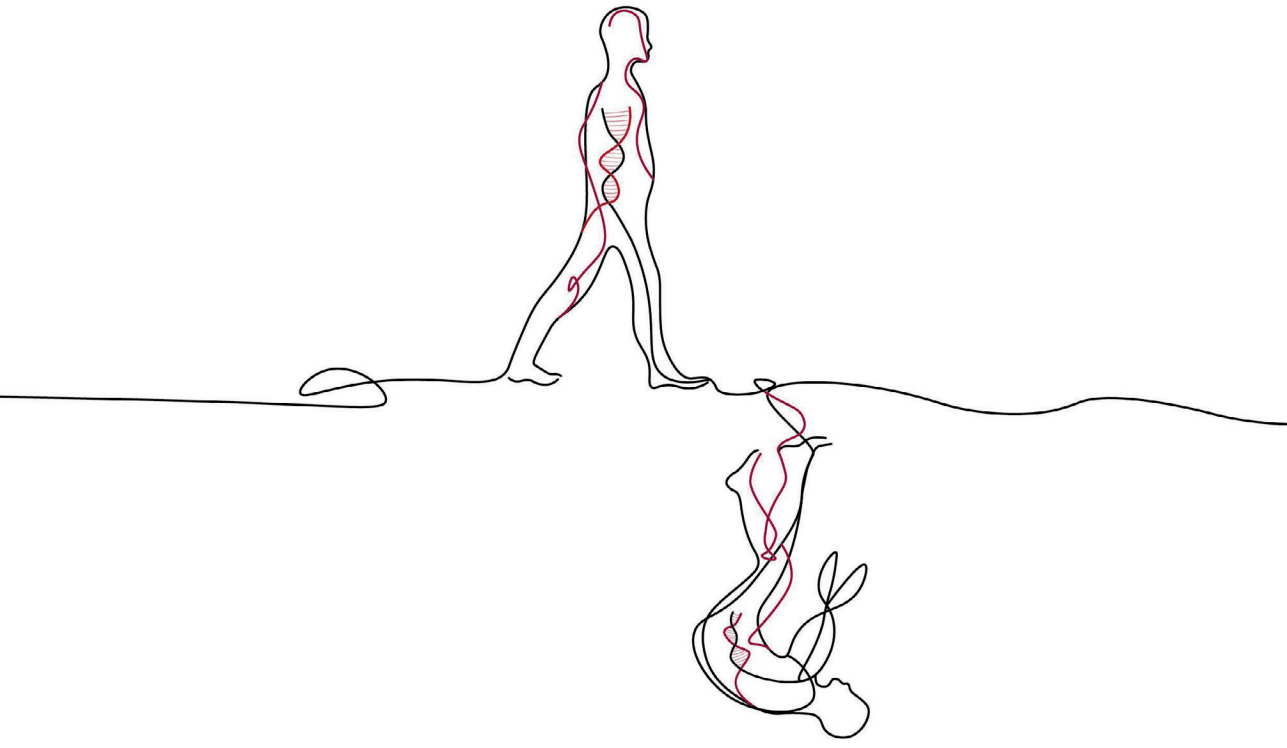
Gonggrijp, B.M.A, van de Weijer, S. G., Bijleveld, C. C., van Dongen, J., & Boomsma, D. I. (2024). Genetic Influence on Social Support: A Twin Study. *Twin Research and Human Genetics*, 1-5.

Gonggrijp, B.M.A, van de Weijer, S. G., Bijleveld, C. C., van Dongen, J., & Boomsma, D. I. (2023). The Co-twin Control Design: implementation and methodological considerations. *Twin Research and Human Genetics*, *26*(4-5), 249-256.

Gonggrijp, B.M. A., van de Weijer, S. G. A., van Dongen, J., Slob, E. M. A., Bijleveld, C. C. J. H., & Boomsma, D. I. (2023). Exploring the Relationships of Crime Victimization with Depression, Anxiety, and Loneliness in Twin Families. *Journal of Developmental and Life-Course Criminology*, *9*(3), 455-482.

Gonggrijp, B.M.A, Silventoinen, K., Dolan, C. V., Boomsma, D. I., Kaprio, J., & Willemsen, G. (2023). The mechanism of assortative mating for educational attainment: a study of Finnish and Dutch twins and their spouses. *Frontiers in Genetics*, *14*, 1150697.

Dankwoord



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