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2023

Integrating genetic data to examine the link between religious attendance and demographic behaviors in the United States

Qi, Jinyuan

Princeton, NJ : Princeton University

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INTEGRATING GENETIC DATA TO EXAMINE THE LINK BETWEEN RELIGIOUS ATTENDANCE AND DEMOGRAPHIC BEHAVIORS IN THE UNITED STATES

Jinyuan Qi

A DISSERTATION
PRESENTED TO THE FACULTY
OF PRINCETON UNIVERSITY
IN CANDIDACY FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

RECOMMENDED FOR ACCEPTANCE
BY THE OFFICE OF POPULATION RESEARCH

Adviser: Dalton Conley

May 2023

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Abstract

The connections between religious attendance and various human behaviors have long fascinated social scientists. Recent genomics and statistical genetics advances in the US, where over 60% of the population maintains religious affiliation, have made it possible to explore the genetic underpinnings of religious attendance and its links to demographic behaviors. This dissertation consists of three chapters that delve into the complexities of religious attendance and human behaviors, highlighting the value of integrating genetic data.

In the first chapter, we examine the shared genetic architecture between religious attendance and diverse demographic traits using genome-wide association studies (GWAS) summary statistics and innovative statistical tools such as Genomic SEM and GWAS-by-subtraction. We create polygenic indices (PGI) for religious attendance in three American longitudinal surveys, uncovering a small yet significant PGI impact on religious attendance. Our findings indicate a negative genetic association between religious attendance and high-risk health behaviors, as well as a positive correlation with improved physical and mental health. Further, our Genomic SEM analysis reveals that religious attendance has a positive genetic effect on the number of children, mediated by education and less risky sexual behavior. This chapter highlights the unique nature of religious attendance in comparison to other forms of social interaction and suggests a potential molecular link between religious attendance and health through cell immunity.

Chapter 2 investigates religious assortative mating and differential fertility among older US adults. Despite declining religious attendance and increasing interfaith marriages, we observe a consistent positive phenotypic correlation among spousal pairs but limited evidence of significant religious assortative mating at the genotypic level. We find that the association between religious attendance and fertility is mediated by education, but no direct genetic effect of religious attendance on fertility is evident.

In Chapter 3, we explore gene-environment interactions with respect to adverse life events, religious attendance, and depressive symptoms. Our research reveals that individuals with varying genetic predispositions to religious attendance respond differently to external stressors. High religiosity PGI and more frequent religious attendance serve as protective factors against depression. Collectively, these chapters offer novel insights into the intricate genetic and phenotypic relationships between religious attendance and demographic behaviors, emphasizing the importance of disentangling the genetic and environmental factors shaping these associations.

Acknowledgements

First and foremost, I would like to express my deepest gratitude to my parents and grandparents, who have been my pillars of support and encouragement throughout my life journey. Their unwavering belief in my abilities and unwavering love and care have provided me with the strength to persevere through challenging times. Their love knows no bounds, and I am truly grateful for everything they have done for me.

I would also like to express my heartfelt gratitude for my dissertation committee, consisting of Dalton Conley, Noreen Goldman, Arun Hendi, Sam Trejo, and Ilana Horwitz. I am immensely grateful for the guidance and mentorship of my advisor and dissertation chair, Dalton. His unwavering support, insightful suggestions, and numerous innovative ideas have greatly enriched the scope and quality of my research. Dalton's incredible open-mindedness and commitment to intellectual exploration have challenged me to think critically and creatively and have nurtured my growth as a scholar. I would also like to express my heartfelt appreciation to Noreen for her invaluable mental support and life guidance during my time at Princeton. As a role model for young demographers, her professionalism, wisdom, kindness, and empathy have been a constant source of solace and inspiration. Noreen and Dalton's kindness and generosity with their time and expertise have been immeasurable, and I am grateful for the detailed edits and feedback they have provided me over the years, which have helped me develop my research and writing skills.

I would like to extend my sincere gratitude to Arun for his invaluable suggestions, advice, and assistance throughout my research journey. His keen insights and thought-provoking questions have enriched my work, and I am grateful for his involvement in my academic pursuits. Special thanks go to Sam for his helpfulness in all sorts of matters, which has made the entire process more manageable and enjoyable. Sam's contributions have also brought new energy to our biosociology team, where I have greatly benefited intellectually. Through Sam, I had the pleasure of meeting Ilana, whose expertise in religion and willingness to lend a helping hand and offer guidance whenever needed have been truly appreciated. I feel incredibly fortunate to have had such exceptional mentors during my academic journey, and I will always cherish their guidance and support.

During graduate school, I had the privilege of working with exceptional professors both in and outside of Princeton. I am grateful for the invaluable help and guidance from Peter Kunstadter, Dean Jamison, David Watkins, Kenneth Wachter, Dennis Feehan, David Cesarini, Anne Case, Marc Ratkovic, Jessica Metcalf, Heather Howard, Alicia Adsera, German Rodriguez, and James Raymo. Their support and inspiration have been instrumental

in my academic pursuits, from their assistance with my courses, general exams, fellowship applications to their guidance in teaching and research.

I am deeply grateful to my department colleagues, staff, and fellow students for creating an engaging and supportive academic environment. Their camaraderie, encouragement, and shared experiences have made my time at Princeton truly memorable and fulfilling. I would like to give a special thanks to Lynne Johnson, our OPR mom, for her big heart, incredible help, warm hugs, and inspirational words that have sent love around and made everyone feel blessed. I am also grateful to Boriana Pratt and Steve Mars for their invaluable help with our Lotka server, databases, and coding problems. Additionally, I would like to thank Mary Lou Delaney, Nancy Cannuli, Valerie Smith, and Wayne Appleton for making OPR my professional home. Their helpfulness and responsiveness are truly appreciated.

During my PhD journey, I faced some health challenges that required timely medical treatments and care from various doctors and nurses across the US. I am deeply grateful for their expertise, kindness, and professionalism, which were crucial to my recovery. I also want to express my heartfelt appreciation to Stanislav Stavarachi and Jessica Wilson, as well as my Colorado family, Chunxiang (May) Chen, Zulong (Liong) Wang, and my Taichi teacher Bing Lee for their in-person care and assistance during my health struggles. Their support was life-saving and deeply appreciated.

Friendship goes a long way, and I am incredibly grateful for the amazing friends I have. Boroka Bo has been like a big sister to me ever since we met at Berkeley, guiding me through some tough times in graduate school. Xuan Jin and Michael Kowen, with whom I have read many medical reports over the last few years, have taught me more than what I could learn from books. Xuan's resilience and strength in the face of adversity have been a source of inspiration. May we learn the lesson of impermanence well and cherish the moments that we can still breathe. Many thanks to all my friends in China and the US, especially Xin (Karl) Liu, Dongmin Ke, Wanru Xiong, Hannah Postel, Emily Miller, Riley Simmons-Edler, and Lady Murasaki for their steadfast support and camaraderie.

Lastly, I want to express my sincere gratitude to the religious communities that have played a significant role in my personal and academic journey. I am especially grateful to Changshou Shifu and Jiantan Shifu, who have provided practical meditation tips and taught me Buddhadharma that have helped me in so many ways. I would also like to thank Yuncong (Melody) Liu for introducing me to Khenpo Tsultrim Lodro's teachings and May for introducing me to Jiejing Shifu and Yongning Shifu, who provided me with heartwarming support in Denver. I am deeply grateful to Master Xuan Hua and his devoted disciples for

their tireless dedication in spreading the transformative teachings of The Shurangama Sutra. If only I had heeded my mother's advice and delved into its wisdom sooner. The experience of reading The Shurangama Sutra for the first time was akin to unearthing a long-sought treasure, providing an indescribable sense of joy and fulfillment. I soon realized that even if I were to devote every remaining moment of my life to studying, learning from, and embodying its teachings, it would still barely scratch the surface of its profound depths. I would also like to thank Yuanquan Shifu, who gave me Master Xuyun's key teachings on Chan practices, 《参禅法要》, before I came to the US. I took it with me wherever I went and have only begun to understand a tiny bit of his teachings.

I am also grateful to the Princeton Zen Club and all the adventures I went through with Aiyu Zheng. Many thanks to other religious communities, including the Chinese Bible study group led by Joseph Ting and Ruth Ting, Trinity Church's prayers for Xuan, vegan food provided at the Jewish Center, and the Office of Religious Life at Princeton, as well as other institutional support from Princeton. Chan Master Thich Nhat Hanh always encouraged us to go back to our own traditions, get rooted, and have faith in our daily practices. Tasting the experiential faith and learning to touch deeply the jewels of my Chan tradition have allowed me to understand and appreciate the values of other traditions better. I am deeply humbled and grateful for all the support, guidance, and inspiration that I have received from these spiritual and religious communities. They have enriched my life in countless ways, and I am honored to be a part of their shared journey.

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Introduction

Religious attendance has long been a significant aspect of American culture, and despite the recent decline in religious affiliation, it continues to shape various aspects of society (Pew Research Center, 2019). The United States remains a predominantly religious nation (Miller, 2008). According to a 2021 Pew Research Center survey on religion and public life in the United States, about 63% of American adults identify as Christians, and another 6% identify with non-Christian faiths such as Judaism, Islam, Hinduism, or Buddhism. Additionally, about 29% of adults identify as religiously unaffiliated or "nothing in particular". However, the percentage of Americans who identify as religiously unaffiliated has been steadily increasing over the past decade.

Religiosity is commonly defined as an individual's commitment to a particular faith or belief system, often measured through religious attendance or involvement in religious activities (Gorsuch, 1984). Studying the associations between religious attendance and various demographic traits in the US is becoming increasingly important to understand its role in shaping individual behavior and societal trends. In this dissertation, we investigate religious attendance among the non-Hispanic white population in the US. With a majority of the population identifying as Christian, church attendance serves as the primary form of religious attendance in our study.

Recent advancements in statistical genetics have paved the way for a more comprehensive understanding of the relationship between religious attendance and demographic traits. By integrating genetic data, researchers can now explore the complex interplay between genetic and environmental factors that contribute to an individual's religious attendance and its association with various outcomes (Plomin et al., 2013). This integration allows for a deeper understanding of the causal mechanisms behind the observed relationships and helps to disentangle potential confounding factors that may otherwise be attributed to environmental influences (Plomin et al., 2013).

The relationship between religious attendance and demographic traits has been the subject of numerous studies, revealing that religious attendance is associated with various aspects of health, well-being, and social integration (Koenig et al., 2001; Lim & Putnam, 2010). In particular, higher levels of religious attendance have been linked to better mental and physical health, as well as lower rates of substance abuse and risky behavior (Koenig et al., 2001). Additionally, religious attendance has been shown to foster social cohesion and civic engagement, contributing to more stable and resilient communities (Lim & Putnam, 2010). Given these associations, understanding the connections between religious attendance and demographic traits through the lens of genetic data is critical for policymakers and

researchers alike, as it provides valuable insights into the potential benefits and challenges that arise from religious involvement in contemporary American society.

This dissertation employs publicly available genome-wide association study (GWAS) summary statistics and utilizes the latest advancements in statistical genetics to explore the potential correlations between religious attendance and a range of demographic characteristics in the United States. We used data sourced from three longitudinal American surveys, namely the National Longitudinal Study of Adolescent to Adult Health (Add Health), the Health and Retirement Study (HRS), and the Wisconsin Longitudinal Study (WLS). By incorporating genetic data into our analysis, we hope to contribute to a better understanding of the complex role that religious attendance plays in shaping individual and societal outcomes. This investigation will shed light on the factors that drive religious attendance and its impact on different aspects of American life, ultimately providing valuable insights for future research and policy development. Through this innovative approach, we seek to expand the current knowledge base and pave the way for a more comprehensive understanding of the interplay between genetics, religious attendance, and demographic traits in the US population.

In Chapter 1, we examine the shared genetic architecture between religious attendance and demographic traits in the United States, using GWAS summary statistics and genotyping data from HRS, WLS, and Add Health. The study uses various newly developed methods, including PRSice2, cross-trait LD score regression, Genomic SEM, and GWAS-by-subtraction, to explore the shared genetic architecture.

In Chapter 2, we investigate religious assortative mating and fertility among US older adults. Specifically, we examine the trend of religious assortative mating across generations, changes in correlations between partners' polygenic index (PGI) of religious attendance, the predictive power of religious attendance PGI on spousal religious attendance and fertility, the genetic correlation between fertility and religious attendance, and the direct and indirect genetic effects of religious attendance on fertility. The study utilizes spousal data from HRS and sibling data from WLS, and employs methods such as descriptive analyses, regression analysis, and Mendelian imputation.

In Chapter 3, we examine the effects of religious attendance on mental health in response to adverse life events. The study aims to answer questions about whether religious attendance increased after the 9/11 terrorist attacks among younger US adolescents and adults and whether more religious individuals had fewer depressive symptoms. Additionally, the chapter

examines whether more religious individuals had fewer depressive symptoms after the death of a spouse and whether religious attendance could help ease the grief of losing a spouse. We utilize Add Health and HRS data and employ methods such as regression discontinuity design, local linear and non-linear parametric models, and non-parametric models. This chapter aims to contribute to a better understanding of the role of religious attendance in coping with adverse life events and its impact on mental health.

To ensure accessibility for social scientists without extensive training in statistical genetics, this dissertation includes a primer at the end of the document. The primer provides a concise overview of relevant concepts and methodologies used throughout the dissertation, offering a brief introduction to statistical genetics for those unfamiliar with the field. In addition, each chapter of the dissertation includes supplementary materials. By offering a primer and supplementary materials, this dissertation aims to make its findings accessible and reproducible for a wide range of social scientists.

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Chapter 1 Exploring the shared genetic architecture of religious attendance and demographic behaviors

1. Introduction

Religiosity is a concept that has been studied extensively in social science. It can be defined as an individual's level of commitment or engagement with religious beliefs and practices (Levin, 1994). Religious attendance, or the frequency with which an individual attends religious services, is a commonly used operationalization of religiosity in social science research (Ellison & George, 1994; VanderWeele, 2017). Previous studies have found that in the US religious attendance is phenotypically associated with many important demographic behaviors, such as health behaviors (Dodor, 2012; Homan & Boyatzis, 2010; Nonnemaker et al., 2006), longevity/mortality (Chida et al., 2009; Idler et al., 2017; Sullivan, 2010), marriage (Lambert & Dollahite, 2006; Thornton et al., 1992), and fertility (Hayford & Morgan, 2008; Marshall & Shepherd, 2018). In demography, studies have often linked religious attendance to fertility and family formation. Some research has suggested that religious attendance is associated with higher levels of fertility (Hayford & Morgan, 2008; Mosher et al., 1992). However, the relationship between religious attendance and fertility is complex, as religious attendance may also be associated with other factors that influence fertility, such as education and societal attitudes toward marriage, childbearing, and family formation.

Studying the genetic architecture of religious attendance is important for the following reasons. Firstly, it helps us understand the biological basis of this complex human trait. Religious attendance is a multidimensional construct that includes beliefs, behaviors, and attitudes toward religion, and it has been linked to various social and health outcomes. By investigating the genetic basis of religious attendance, we can gain insight into the biological mechanisms that underlie these outcomes. Moreover, religious attendance is a complex social and behavioral phenomenon that is shaped by both genetic and environmental factors. Disentangling the relative contributions of these factors is crucial to understanding the development and expression of religious attendance. However, the study of social and behavioral processes is inherently challenging due to the presence of genetic confounding, which occurs when genetic factors influence both the exposure of interest and the outcome of interest (Fletcher & Lehrer, 2011; Harden, 2021). This confounding can lead to biased estimates of the true relationship between religious attendance and other traits. For instance, previous demographic literature on the positive correlation between religious attendance and higher fertility among American women (Mosher et al., 1992) may be confounded by shared genetic architecture between religious attendance and fertility that was not accounted for.

Without using genetic data, genetic influences on polygenic traits are likely to be unobserved confounders because of pleiotropy, a phenomenon in which a single genetic locus affects two

or more distinct phenotypic traits (Stearns, 2010). Numerous genome-wide association studies (GWAS) have revealed that pleiotropy is the norm for complex traits, and many genetic loci could be associated with multiple seemingly distinct traits (Solovieff et al., 2013). To gain insights into causal analyses and gene-environment interactions of complex traits with pervasive pleiotropy, it is important to integrate genetic data and explore the shared genetic architecture and molecular mechanisms. Understanding the underlying genetic architecture of religious attendance can provide insights into the biological mechanisms that drive religious behaviors and beliefs, which have profound effects on individual behavior, social institutions, and cultural values. In this chapter, we constructed polygenic indices (PGIs) of religious attendance. These PGIs were then utilized in the subsequent chapters. We conducted multivariate analyses using publicly available GWAS summary statistics and newly developed statistical tools such as LDSC, genomic SEM, and GWAS-by-subtraction to explore the shared genetic architecture of religious attendance and commonly measured demographic behaviors.

2. Literature Review

The development of high-throughput single-nucleotide polymorphism (SNP) arrays enabled the genotyping of hundreds of thousands of SNPs simultaneously and gave rise to the genome-wide association study (GWAS), which tests the association between each SNP and

phenotypes (Risch & Merikangas, 1996). Based on recent large-scale GWAS findings of unrelated individuals, the fourth law of behavioral genetics was proposed: "A typical human behavioral trait is associated with very many genetic variants, each of which accounts for a very small percentage of the behavioral variability (Chabris et al., 2015)."

There is currently only one GWAS on religious attendance from a study (Day et al., 2018) measuring loneliness and social interaction. Religious attendance was measured as a binary variable of regular participation in religious groups (once a week or more) from UK Biobank data. The heritability estimated from this study (Day et al., 2018) for religious attendance is 4.6%, and the researchers found 18 variants that were associated with religious attendance (P $<5 \times 10^{-8}$); one signal, rs9837520, was associated primarily with religious attendance (P $=2.6 \times 10^{-8}$) and was correlated with reported signals for inflammatory bowel disease ($r^2 = 1$) and educational attainment ($r^2 = 0.75$). The study also discovered that the frontal cortex (P $=6.2 \times 10^{-6}$), and in particular the anterior cingulate cortex (P $=1.1 \times 10^{-4}$) was the most relevant cell and tissue type for the underlying process regulating religious attendance (Day et al., 2018). The anterior cingulate cortex is located in the medial frontal lobe and regulates autonomic and endocrine functions and plays a crucial role in emotional learning, initiation, motivation, and goal-directed behaviors (Devinsky et al., 1995).

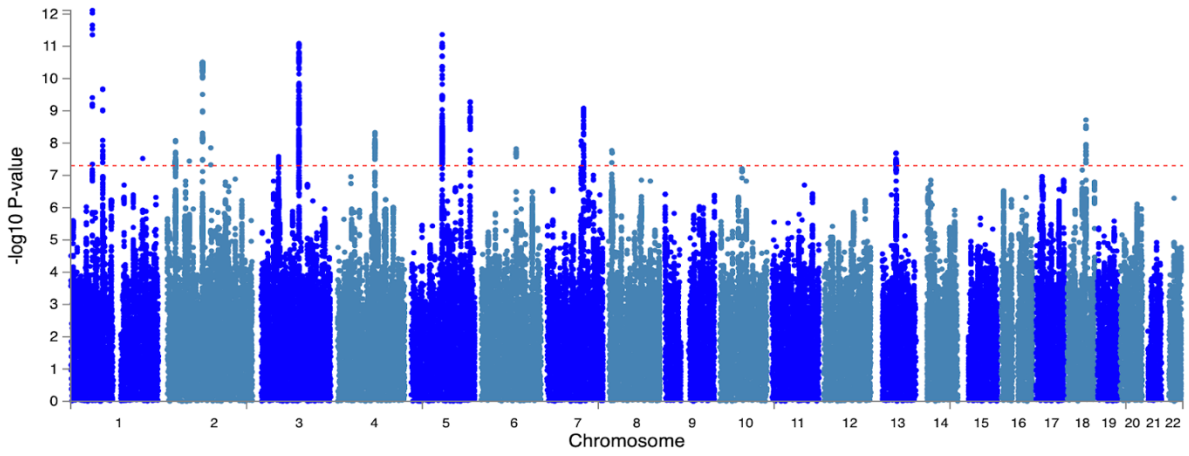


Figure 2.1 - Manhattan plot for religious attendance from the study 'Elucidating the genetic basis of social interaction and isolation' (Day et al., 2018). The red horizontal dotted line denotes genome-wide significance (5×10^{-8}, and Figure D.a.1 in Supplementary Materials shows 45 genes identified from the gene-based test of religious attendance GWAS.

The GWAS conducted by Day et al. (2018) used a linear mixed model to perform preliminary genetic correlation analyses between religious attendance and 115 traits related to social interaction. Given that most human behavioral traits are highly polygenic, it is plausible that religious attendance shares substantial genetic correlations with various traits beyond social interaction. With recent advancements in genome-wide association study (GWAS) techniques, it is now possible to estimate these genetic correlations between religious attendance and virtually any other trait using publicly accessible data sources (van Rheenen et al., 2019). As the number of available GWAS summary statistics continues to grow, we expect to identify additional genetic correlations between religious attendance and other

variables, including commonly measured health behaviors and reproductive behaviors in demography, such as age at first birth and the number of everborn children.

Further, since GWAS requires considerable statistical power to discover genetic variants with a very small impact on the phenotype (van der Sluis et al., 2013), independent data with a sample size comparable to the UK Biobank (>450K) have not been used to replicate GWAS on religious attendance with individual loci. Nevertheless, we can use unrelated samples from the US, where Christianity is also a major religion, to test and validate the GWAS from the UK Biobank data. We used three American longitudinal surveys to construct PGIs to predict religious attendance among non-Hispanic white Americans and compared the methods and results with a recently built PGI repository (Becker et al., 2021), standardizing the methodology of PGI construction. Given the different social context in the US, we hypothesized that the marginal R^2 [the measurement of the predictability] inferred from the PGI of religious attendance in US longitudinal datasets (as testing datasets) would be lower than the marginal R^2 (1%) observed in the UK Biobank testing data and the SNP heritability (4.6%) found in the original UK Biobank training data (Day et al., 2018; Becker et al., 2021).

Genomic structural equation modeling (SEM) (Grotzinger et al., 2019) can be used to model multivariate genetic associations among religious attendance and selected phenotypes to

explore the shared genetic architecture further. Previous demographic studies have observed that more religious individuals have, on average more children than less religious ones (Fieder & Huber, 2016; Frejka & Westoff, 2008). However, other studies have found mixed or null effects, suggesting that the relationship between religious attendance and reproductive outcomes is complex and likely influenced by a range of factors such as cultural norms and social context (Derosas & Van Poppel, 2006; Lehrer, 2004; Zhang, 2008). Although education has frequently been employed as a control variable when examining the association between religious attendance and fertility, the extent to which education mediates this relationship remains uncertain (Adsera, 2006; Hayford & Morgan, 2008; Philipov & Berghammer, 2007). One study by Barber (2001) found that higher levels of religious involvement were associated with a later age at first birth among American women. In terms of risky sexual behaviors, some studies have found that higher levels of religiosity are associated with a lower likelihood of engaging in premarital sex or using contraception (Bearman & Brückner, 2001; Regnerus et al., 2004). However, other studies have found that the relationship between religiosity and risky sexual behaviors is more nuanced and may depend on factors such as gender and denomination (Meier & Allen, 2009). Overall, the relationship between religious attendance and reproductive outcomes is complex and likely mediated and influenced by a range of factors. Genomic SEM provides a tool to model complex mediation using GWAS summary statistics, all of which may not be available in a

single survey, to examine whether religious attendance has direct and indirect effects on fertility.

In addition, the genomic SEM can also model common latent factors that cannot be directly measured. We conducted an exploratory factor analysis to identify the common factor(s) between religious attendance and other psychiatric traits (e.g., depression, feeling worried) in order to measure the shared genetic architecture between religious attendance and mental health indicators, as previous studies indicated that religious involvement has been found to be positively associated with better mental health outcomes, including lower levels of depression and anxiety (Levin & Chatters, 1998; Rosmarin & Koenig, 1998). Further, GWAS-by-subtraction analysis using genomic SEM was conducted to elucidate the molecular mechanism of religious attendance (Demange et al., 2021). In the initial GWAS study on loneliness, researchers not only investigated religious attendance but also carried out two distinct GWAS analyses focusing on weekly participation in sports clubs/gyms and pubs/social clubs (Day et al., 2018). Research has shown that religious attendance is associated with a greater sense of belonging and social support compared to participation in other social activities (Ferraro & Kelley-Moore, 2000; Strawbridge et al., 1998). On the other hand, participation in other social activities such as sports clubs/gyms and pubs/social clubs may provide individuals with opportunities to interact with a wider range of people who engage in the same entertaining activities but may not necessarily share similar values or

beliefs. As a result, we hypothesized that the genetic architecture underlying religious attendance could be different from that of other social activities.

3. Data and Methods

The UK Biobank has collected genetic information from half a million inhabitants of the UK with a wide range of phenotypic information. Since the only genetic study of religious attendance (Day et al., 2018) uses UKBiobank data for genetic discovery, we used the publicly available GWAS summary statistics of religious attendance from the original study and GWAS summary statistics of other phenotypes from two publicly available data sources: Neale's Lab LDSC Sumstat Files of the UKBiobank study and GWAS summary statistics from the NHGRI-EBI GWAS catalog (Buniello A et al., 2019). The discovery study has 66,259 cases and 386,043 controls regarding whether the respondents attended religious groups once a week or more often. Two other GWAS on regular participation in sports clubs/gyms [135,060 cases and 317,242 controls] and regular participation in pubs/social Clubs [124,047 cases, 328,255 controls] from the original study were used for GWAS-by-subtraction analysis.

Genotyping data and religious attendance variables were obtained from three longitudinal American surveys - The Health and Retirement Study (HRS) (The University of Michigan, 2020), The Wisconsin Longitudinal Study (WLS) (Herd et al., 2014), and The National

Longitudinal Study of Adolescent to Adult Health (AddHealth/ADH) (Harris, Kathleen Mullan, 2018). To construct the PGIs of religious attendance, samples were restricted to respondents with complete genetic data and relevant phenotypic data, i.e., at least one wave of valid response(s) to questions about religious attendance. Detailed information about how the religious attendance questions were coded for each study is available in Supplementary B. Since the original GWAS study only used white Europeans, the samples used in this study were restricted to non-Hispanic European ancestry.

The Health and Retirement Study (HRS) (The University of Michigan, 2020) is a longitudinal study focusing on middle-aged and elderly Americans living in private households. This chapter used 12 waves from the year 1992 to 2018 to construct religious attendance phenotypes. Compared to HRS, the Wisconsin Longitudinal Study (WLS) (Herd et al., 2014) has a relatively homogeneous sample of Americans who graduated from Wisconsin high school in 1957. Four waves of data (1957, 1993, 2004, and 2011) were used for the PGI analysis. The National Longitudinal Study of Adolescent to Adult Health (AddHealth/ADH) (Harris, Kathleen Mullan, 2018) has a much younger sample of adolescents who were in grades 7-12 during the 1994-95 school year. Four waves (1994-5, 1996, 2001-2, 2008-9) were used for PGI construction.

Figure 3.1 Proportion of respondents who attended religious activities at least weekly among all and genotyped non-Hispanic European samples across the year of interview

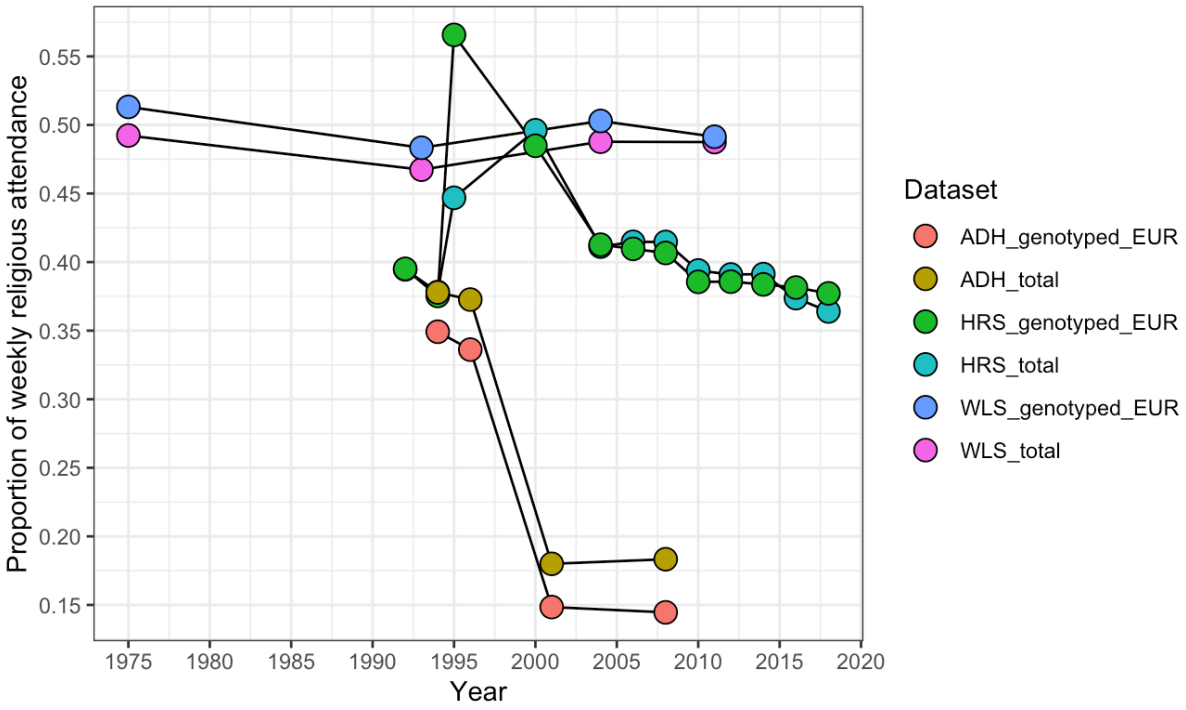


Figure 3.1 illustrates the percentage of survey respondents who reported attending religious activities at least once a week, as recorded across the interview years. The WLS sample had the highest overall religious attendance, around 50%, which indicates a very prevalent social norm of going to church weekly. In contrast, religious attendance for ADH cohorts dropped to less than 20% around age 18 in the third and fourth waves when they left home for college. Sample sizes for HRS before 2004 were smaller, resulting in large fluctuations. The estimates for HRS indicate a decreasing trend of religious attendance in recent years. In general, the difference between the genotyped non-HIispanic European sample and the total sample is not large, but the difference may increase among younger cohorts, as ADH trend lines suggest. For additional information about the measurement of religiosity, including data related to religious affiliation and importance, please refer to Supplementary A. The main PGI analysis

employs religious attendance as a proxy measure of religiosity, given it is the most consistently measured variable of religiosity with the best data availability.

We used the cross-trait Linkage Disequilibrium (LD) Score regression (B. Bulik-Sullivan et al., 2015a; B. K. Bulik-Sullivan et al., 2015b) to compute the overall genetic correlations between religious attendance and other demographic and behavioral traits. Using LD score regression, we can estimate the genetic covariance of two traits from the product of Z scores for the two traits. This approach is robust to sample overlaps in GWAS. Since the overall genetic correlation between two traits only describes the average effect of pleiotropy across all causal loci, the underlying regional architecture of the genetic correlation can vary widely. We also used ρ-HESS(Heritability Estimation from Summary Statistics) (Shi et al., 2017) to calculate local genetic correlations at a small region in the genome on the selected trait pairs with consistently strong overall genetic correlations.

The overall genetic correlation provides an estimate of the shared genetic information across highly polygenic outcomes. Given pervasive pleiotropy, these genetic correlations not only provide results but also serve as data that can be modeled to examine the system of relationships and better understand the data-generating process of these correlations. Genomic Structural Equation Modeling (genomic SEM) (Grotzinger et al., 2019) involves using structural equation modeling to estimate genetic covariance matrices, which enables

users to explore relationships between traits that may be challenging to measure in the same sample. For example, bipolar disorder and schizophrenia will not be assigned to the same person as only one or the other can be diagnosed based on the patient's clinical presentation. However, with genomic SEM, the shared genetic architecture of bipolar disorder and schizophrenia can be modeled using GWAS summary statistics. Therefore, genomic SEM provides the opportunity to model these rare and even mutually exclusive traits, offering a flexible framework for estimating a limitless number of models using publicly available GWAS summary statistics.

We utilized genomic SEM to conduct a mediation analysis to determine the extent to which the relationship between religious attendance and fertility is mediated by education. Further exploration using longitudinal surveys of this topic can be found in the second chapter titled "Religious assortative mating and differential fertility among US older adults". For the mediation modeling, we used summary statistics from GWAS studies on fertility (Barban et al., 2016; Linnér et al., 2019) and education (Okbay et al., 2022). Additionally, to prepare for the investigation in the third chapter ("Gene-environment interactions: adverse life events, religious attendance, and mental health"), an exploratory factor analysis was conducted on religious attendance and mental health indicators. This analysis used additional GWAS studies on depression, worry, neuroticism (Nagel et al., 2018), and PTSD (Nievergelt et al., 2019).

In the original UK Biobank survey, participants were asked about their religious attendance along with two other social activities - participation in sports clubs/gyms and pubs/social clubs. To better understand the genetic associations specific to religious attendance, we conducted a GWAS-by-subtraction analysis (Demange et al., 2021) to identify unique genetic variants that are associated with religious attendance after accounting for participation in sports clubs/gyms and pubs/social clubs. For example, while participating in religious activities and attending sports clubs/gyms both involve engaging in a social activity with a group of individuals who share a common interest, the two activities differ in their nature and purpose. Through GWAS-by-subtraction, we can identify the latent factor of 'religious-without-sports/gym' as well as the common latent factor representing both social interactions. This approach enables us to capture the shared genetic influences related to physical activity, such as interests, motivation, and social bonding in group activities. Additionally, we performed functional mapping, biological annotation, and enrichment analysis using MAGMA generalized gene analysis (Leeuw et al., 2015) and FUMA (Watanabe et al., 2017) to gain further insights into the biological mechanisms that may be involved in the relationship between genetics and religious attendance.

4. Results

a. PGI prediction of religious attendance

Table 4.a.1 displays the results of using PGI to predict religious attendance in three American longitudinal surveys. The analysis shows that the marginal R^2 of PGI was 0.85% in WLS, 1.0% in HRS, and 1.51% in ADH. Notably, the ADH cohort has a younger age range and a smaller proportion of respondents who regularly attend religious activities compared to WLS and HRS. The full model includes principal components, a first-degree or second-degree polynomial for birth year, sex, and the interaction of birth year and sex. Including the second-degree polynomial in the last column generally increases the explained variance, particularly in HRS. As HRS respondents have a wider range of birth cohorts than the other two surveys, more than 7% of the variance can be explained by birth year, sex, and principal components. The variance explained by covariates is lowest among ADH respondents.

We coded religious attendance phenotypes from multiple waves differently in binary and continuous forms and controlled for various sets of covariates for PGI construction. Supplementary Table B.1 presents the complete results. The following Table 4.a.1 shows the results from the binary coding of weekly religious attendance. All predictions are statistically significant ($P < 1 \times 10^{-3}$), which confirms previous findings that religious attendance has a heritable component.

Table 4.a.1 - Best PGI prediction of religious attendance among replication samples

	Covariates	**PGI + birthyear*sex + PCs**		**PGI+ byear*sex + $byear^2$*sex + PCs**	
Dataset	**Sample Size (N) F = Female**	**Marginal PGI R^2 (%)**	**Full Model R^2 (%)**	**Marginal PGI R^2 (%)**	**Full Model R^2 (%)**
WLS	8,997 (F:4,686)	0.85	5.74	0.84	5.91
HRS	10,811 (F:6,198)	0.98	8.08	1.00	8.54
ADH	5,969 (F:3,157)	1.51	3.93	1.50	3.97

b. Genetic Correlation Exploratory Data Analysis

Out of approximately 700 traits from the UK Biobank data, 320 traits pass a conservative Bonferroni correction threshold ($P < 5 \times 10^{-5}$) and show statistically significant genetic correlations. The three figures below present the overall genetic correlation between religious attendance and selected demographic traits that are of common interest to social scientists. Supplementary Table C.a.1 contains the complete list of the 320 statistically significant traits.

An overall genetic correlation (denoted rG here) is the proportion of variance that two traits share due to genetic causes, which can help us estimate the degree of pleiotropy. Figure 4.b.1 shows that more frequent religious attendance is negatively associated with high alcohol intake frequency, ever smoking, maternal and household smoking, poor general health, and

more reported non-communicable health conditions, such as diabetes, high blood pressure, and heart attacks.

Figure 4.b.1 - Overall genetic correlation (rG) between religious attendance and health-related traits

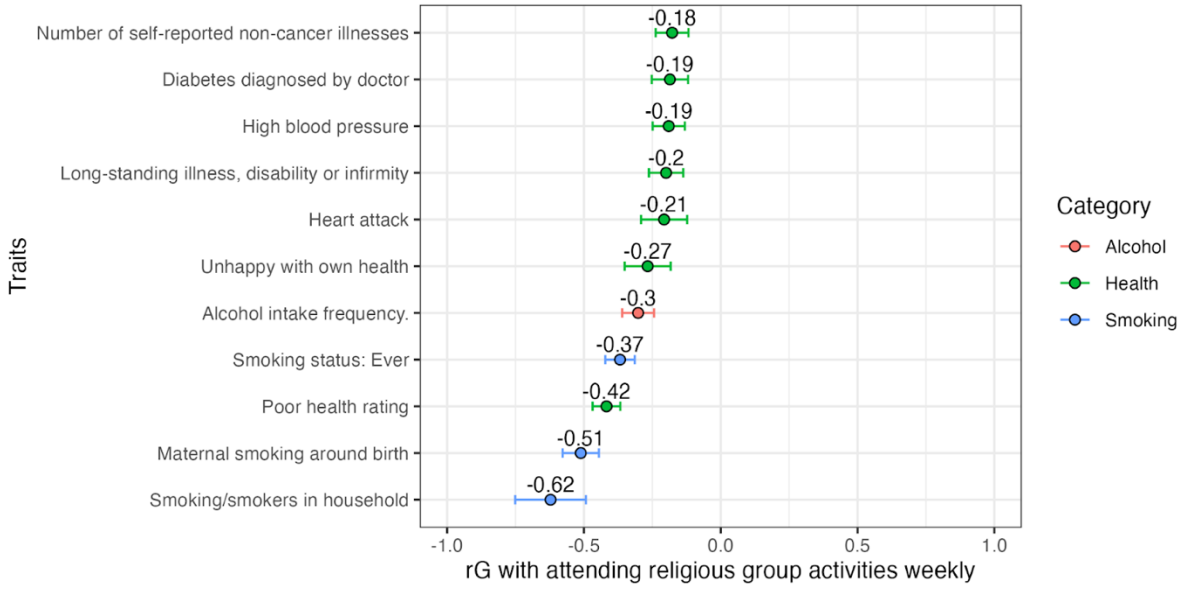
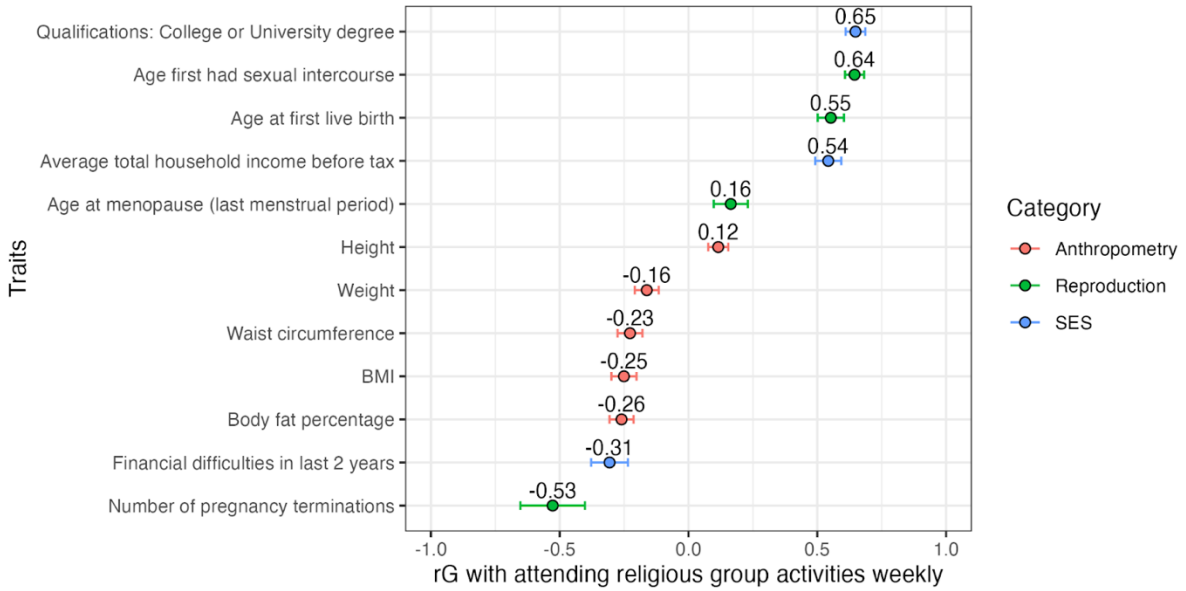


Figure 4.b.2 shows strong positive genetic correlations (>0.5) between religious attendance and indicators of reproductive behaviors, such as higher age at first sexual experience and higher age at first live birth. On the other hand, there was a strong negative correlation between high religious attendance and the number of pregnancy terminations. Religious attendance was also found to be positively correlated with better education, higher household income, and fewer financial difficulties, indicating a higher socioeconomic status. In addition, the anthropometric measures in red reveal that religious attendance is positively correlated with height and negatively correlated with weight, BMI, waist circumference, and body fat percentage.

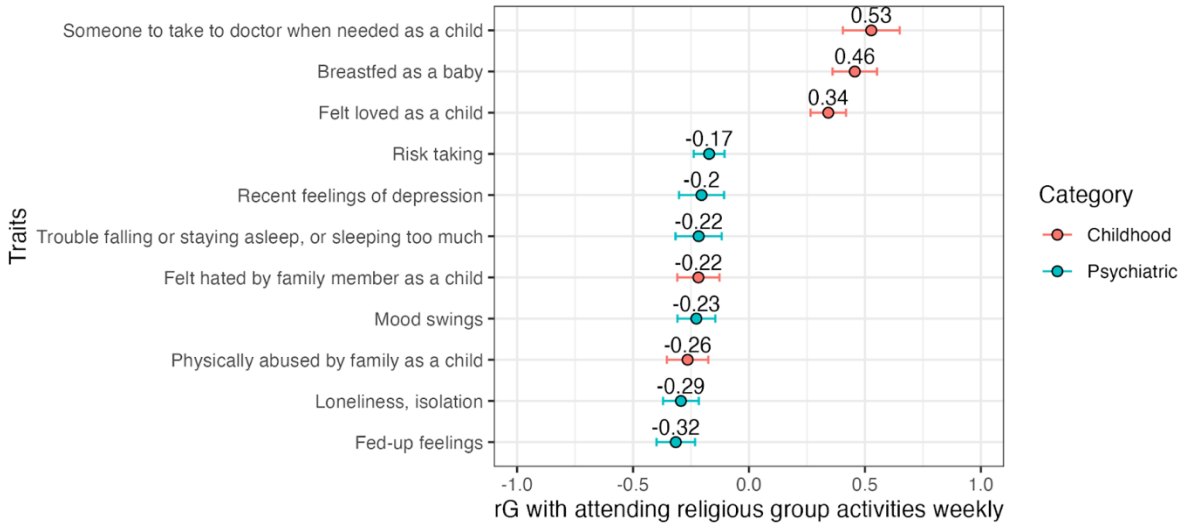
Figure 4.b.2 - Overall genetic correlation (rG) between religious attendance and anthropometry, SES & reproduction



Regarding the genetic correlation between religious attendance and psychiatric traits presented in Figure 4.b.3, positive correlations are observed with positive experiences in childhood, such as having someone to take the child to the doctor and feeling loved as a child. It is possible that more religious parents provide better care or a more stable parenting environment for their children, which may play a role in explaining these positive correlations. On the other hand, religious attendance is negatively associated with risk-taking and various negative emotions, including depression, trouble falling asleep, mood swings, loneliness, and feelings of being fed up. As proposed by Cheverud's Conjecture (Cheverud, 1988), genetic correlations typically mirror phenotypic correlations. Therefore, the negative genetic correlation between religious attendance and high-risk health behaviors may indicate genetic overlaps that could lead to religious attendance being associated with better physical

and mental health phenotypically. We did not find any significant results for local genetic correlation analysis, suggesting that the overall genetic correlations result from the accumulation of small genetic effects across the whole genome. Supplementary C.b presents an example of the local genetic correlation between religious attendance and depression.

Figure 4.b.3 - Overall genetic correlation (rG) between religious attendance and psychiatric traits



c. Genomic SEM

Figure 4.c.1 shows that religious attendance and the number of everborn children appear almost independent, with a near-zero overall genetic correlation. However, religious attendance is positively correlated with years of education and age at first birth and negatively associated with the number of sexual partners. To examine the extent to which religious attendance affects fertility through education, Figure 4.c.2 presents a path diagram

showing directional associations. The genetic path between religious attendance and the number of everborn children, denoted in blue, is significantly positive (0.20, with a standard error of 0.06), suggesting a direct positive effect beyond indirect effects through other paths. However, the total effects of religious attendance on fertility are complex due to the indirect pathways mediated by education, the number of sexual partners, and the age at first birth. For example, while religious attendance is positively associated with education, which is in turn positively associated with fertility. However, more years of education is positively associated with the age at first birth, which is in turn negatively associated with the number of children. Furthermore, the negative correlation between religious attendance and the number of sexual partners suggests an overall negative effect on the number of children. As the positive effects are offset by negative effects through mediation, the total effect of religious attendance on fertility is close to zero. This modeling exercise demonstrates that genomic SEM can effectively test complex theories by modeling the system of direct and indirect effects, which helps researchers to better understand the intricate relationships among different variables.

We estimated the parameters of SEM by minimizing the discrepancy between the model-implied genetic covariance matrix ($\sum(\theta)$) and the empirical/observed covariance matrix (S), which was first estimated by using LD score regression on GWAS summary statistics (Grotzinger et al., 2019). The metrics on the right side of the path diagrams help us evaluate

the fit, including the standardized root mean square residual (SRMR), the model χ^2 , the Akaike Information Criterion (AIC), and the Comparative Fix Index (CFI).

According to Grotzinger et al. (2019), the model indices should be considered concurrently. SRMR was calculated as the standardized root mean squared difference between $\sum(\theta)$ and S, and a lower value [0.014] less than 0.05 indicates a good fit, i.e., a smaller discrepancy between the two covariance matrices. Similarly, we use the model χ^2 to compare two matrices with a lower value indicating a better fit. The non-significance indicates the two matrices do not significantly differ from each other. In addition, AIC balances fit with parsimony, which was calculated as AIC =$\chi^2 + 2fp$, where fp is the number of free parameters [fp = 13] in the mediation model. Lower AIC values indicate better model fit. CFI tests approximate model fit by comparing the fit of the proposed model to the fit of an "independence" model that estimates genetic variances of all phenotypes but assumes all genetic covariances to be zero when $\sum(\theta)$ is diagonal. The following formula was used to calculate CFI: CFI = $\frac{f(\text{indepdence model}) - f(\text{proposed model})}{f(\text{indepdence model})}$, where $f = \chi^2$ -d.f.. With a CFI value (0.998) larger than 0.95, the mediation model proposed in Figure 4.c.2 is again considered as a good fit.

Figure 4.c.1 Genetic correlation heatmap for genomic SEM of religious attendance and fertility

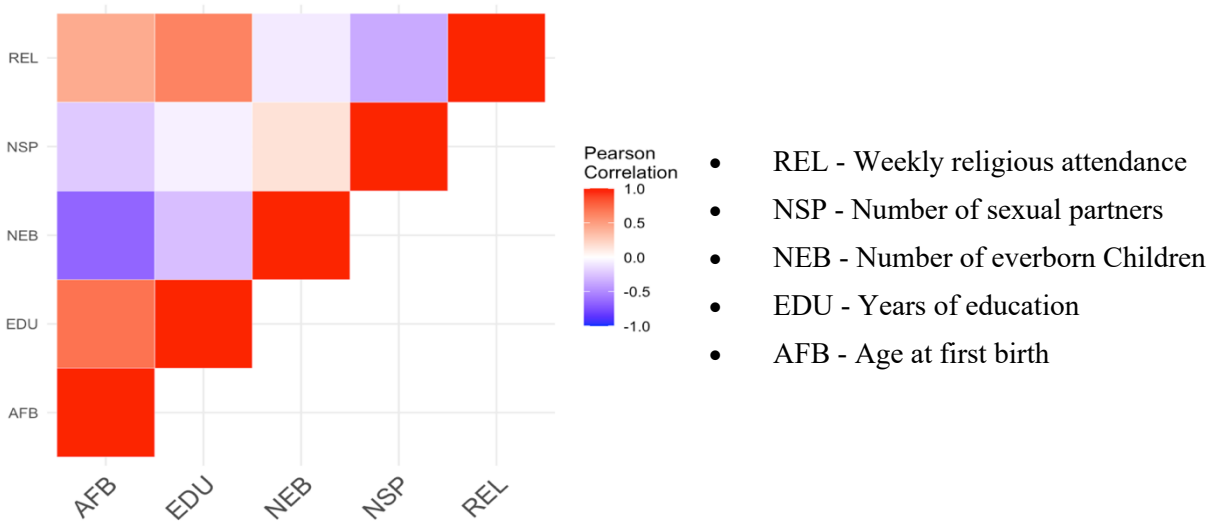
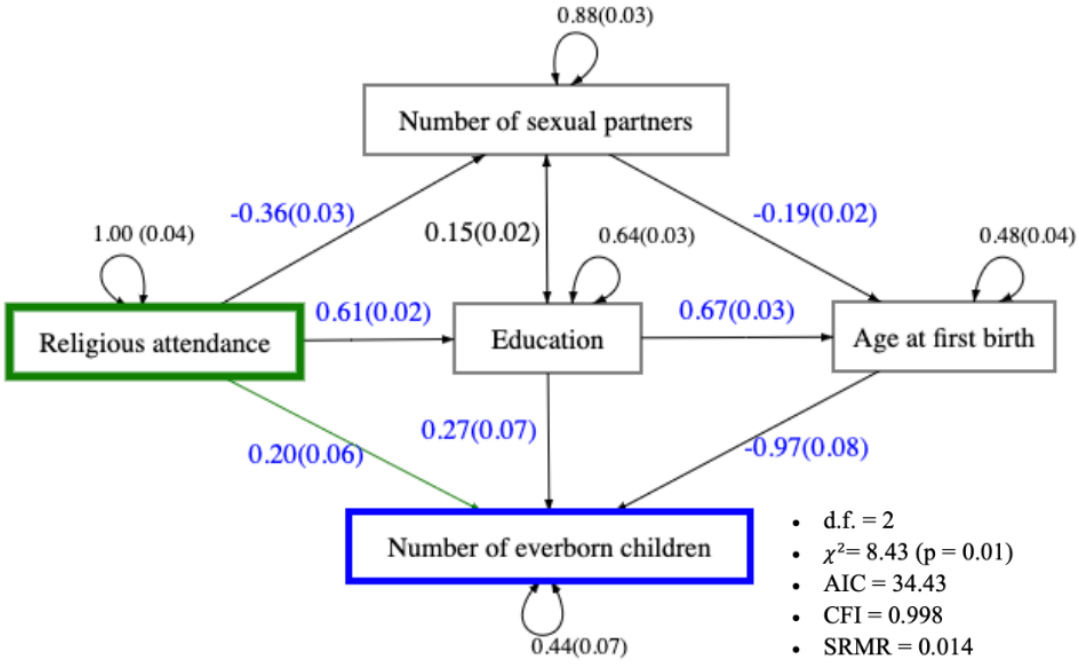


Figure 4.c.2 - Genomic SEM of religious attendance and fertility



We conducted an exploratory factor analysis on religious attendance and mental health indicators. Figure 4.c.3 shows a negative association between religious attendance and other indicators, while Figure 4.c.4 presents a two-factor model that has model indices on the right side of the figure (χ^2= 20.10, AIC = 52.10, CFI = 0.9996, and SRMR = 0.0221). Even

though the model χ^2 is significant at 0.01 level, the model-implied covariance matrix closely approximates the empirical genetic covariance matrix as indicated by the high CFI value and low SRMR value, which suggest an excellent fit. The two-common factor provides a better fit than a single-factor model for all six traits shown in Figure 4.c.4, indicating that the two latent variables not directly measured could represent common concepts that are measured by religious attendance and five other psychiatric traits.

The blue color in the diagram represents the direct pathways between the first latent variable and PTSD, loneliness, religious attendance, depression, and neuroticism, while the green color denotes the direct pathways between the second latent variable and religious attendance, depression, neuroticism, and worry. The high factor loadings on PTSD, loneliness, and depression for the first latent variable suggest that it may measure a common concept of social interaction, whereas the second latent variable could indicate a common type of personality, as it has high factor loadings on neuroticism and worry. The two latent factors are positively associated with each other.

Religious attendance is a distinct measurement according to both Figures 4.c.3 and 4.c.4, as it is negatively correlated with all other psychiatric traits, with different signs of factor loadings for the two common factors. While the two-common factor model can help illuminate comorbidity across psychiatric disorders, it does not fully clarify the relationship between

religious attendance and depression. Therefore, further investigation is needed to better understand this relationship. However, the positive association with the first latent factor suggests that the social interaction aspect of religious attendance may help reduce the risk of depression. In the next part, a GWAS-by-subtraction analysis further explores how the measurement of religious attendance is distinct from other indicators of social interaction.

Figure 4.c.3 Genetic correlation heatmap for genomic SEM of religious attendance and mental health

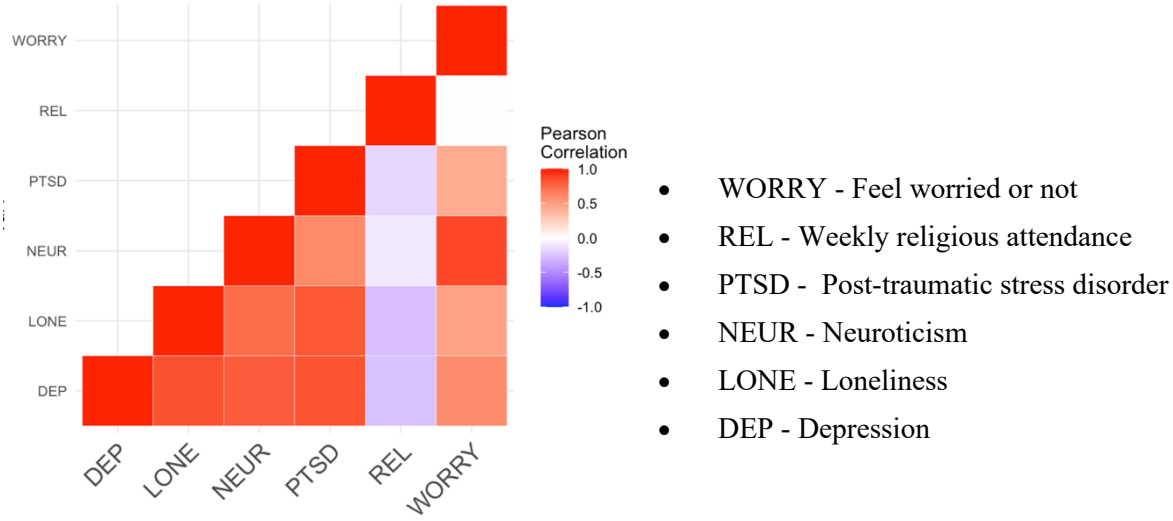
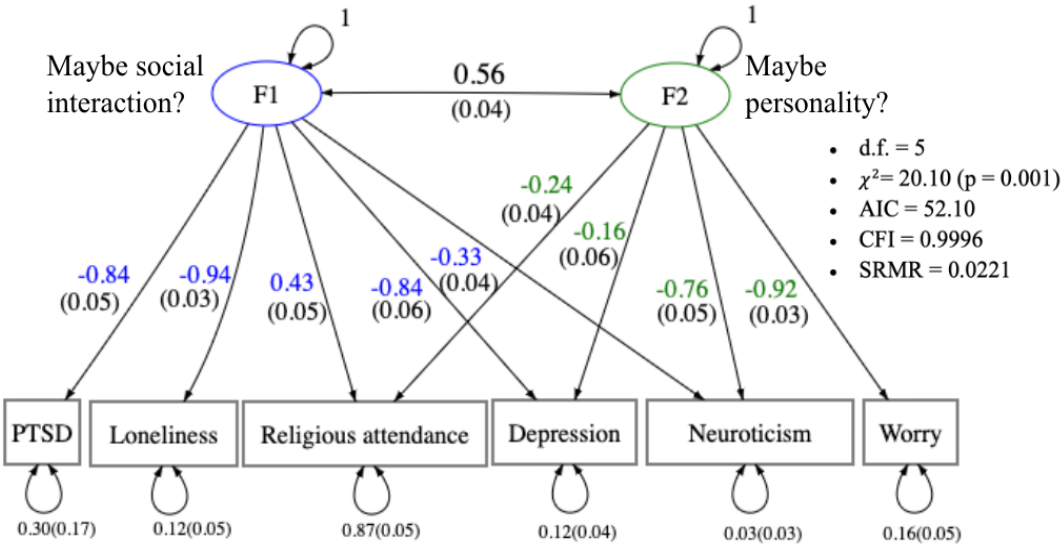


Figure 4.c.4 - Exploratory factor analysis of religious attendance and mental health



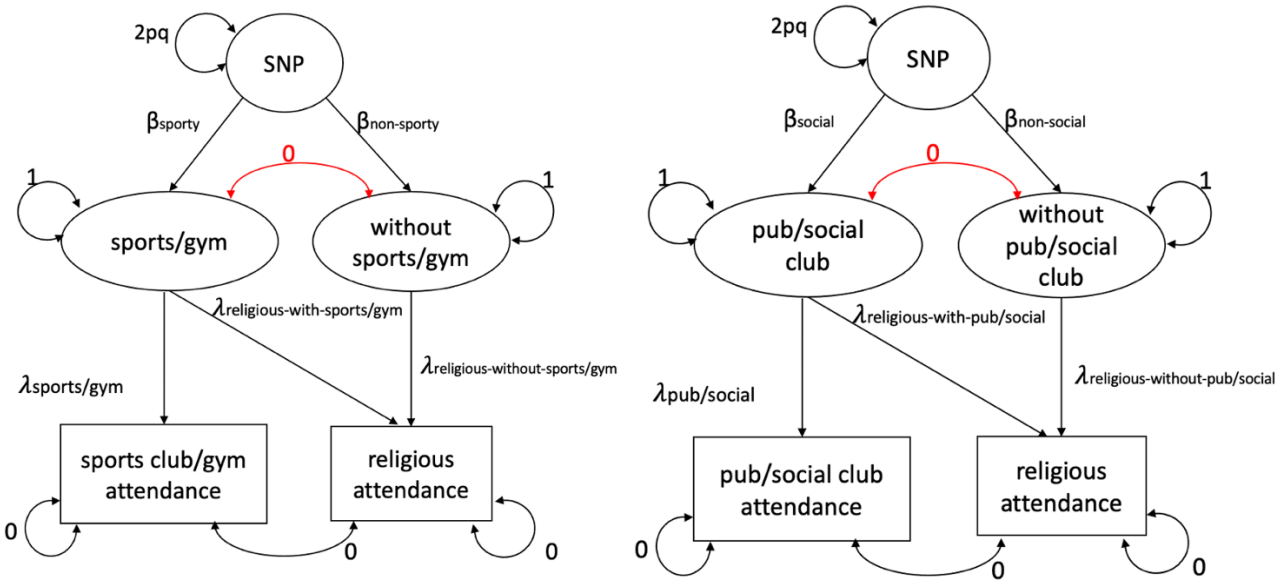
d. GWAS-by-subtraction

Figure 4.d.1 illustrates the two genomic SEM models used in the GWAS-by-subtraction analysis, applying the methods proposed by Demange et al. (2021). The first Genomic-SEM model applies to GWAS summary statistics (Day et al., 2018) for weekly participation in religious activities, sports clubs/gyms, and pubs/social clubs. Using the first model on the left as an example, weekly attendance at religious services and sports clubs/gyms is regressed on a common latent factor representing shared social interaction that leads to regular participation in both sports and religious activities. The second latent factor represents the residual genetic variance in religious attendance after regressing out the variance related to the first latent factor.

The main assumption denoted in red is that these two latent factors are independent of each other. Therefore, the "religious-without-sports/gym" factor represents the genetic variation in religious attendance that is not accounted for by the first common social interaction factor. The two latent factors are then regressed on each SNP with variance fixed to the value of 2pq [p = reference allele frequency, and q is alternative allele frequency, based on 1000 Gene project phase 3(Auton et al., 2015)]. The beta estimates of each SNP for the two latent factors provide two GWAS summary statistics on the two latent factors, respectively. In addition, we conducted gene-based tests using MAGMA (Leeuw et al., 2015) and enrichment analyses

using FUMA (Watanabe et al., 2017) to elucidate molecular mechanisms of religious attendance.

Figure 4.d.1 GWAS-by-subtraction Genomic-SEM models



MAGMA (v1.6) assigned SNPs to the protein-coding genes, and 45 genes from the original religious attendance study passed genome-wide significance [Supplementary Figure D.a.1], which was set at $0.5/18884 = 2.648 \times 10^{-6}$. Figure 4.d.2 shows a gene expression heatmap of the 44 genes from the positional mapping of SNPs to genes up to 10kb and enrichment tests of differentially expressed genes (EDG). Since MAGMA gene-property analysis was performed using the full distribution of SNP p-values, the genes that passed genome-wide significance could be different from the genes from positional mapping enrichment tests. We also performed tissue expression analysis using MAGMA for 53 specific tissue types, which are available in Supplementary Figure D.a.2.

Figure 4.d.2 - Gene expression heatmap of religious attendance (44 genes)

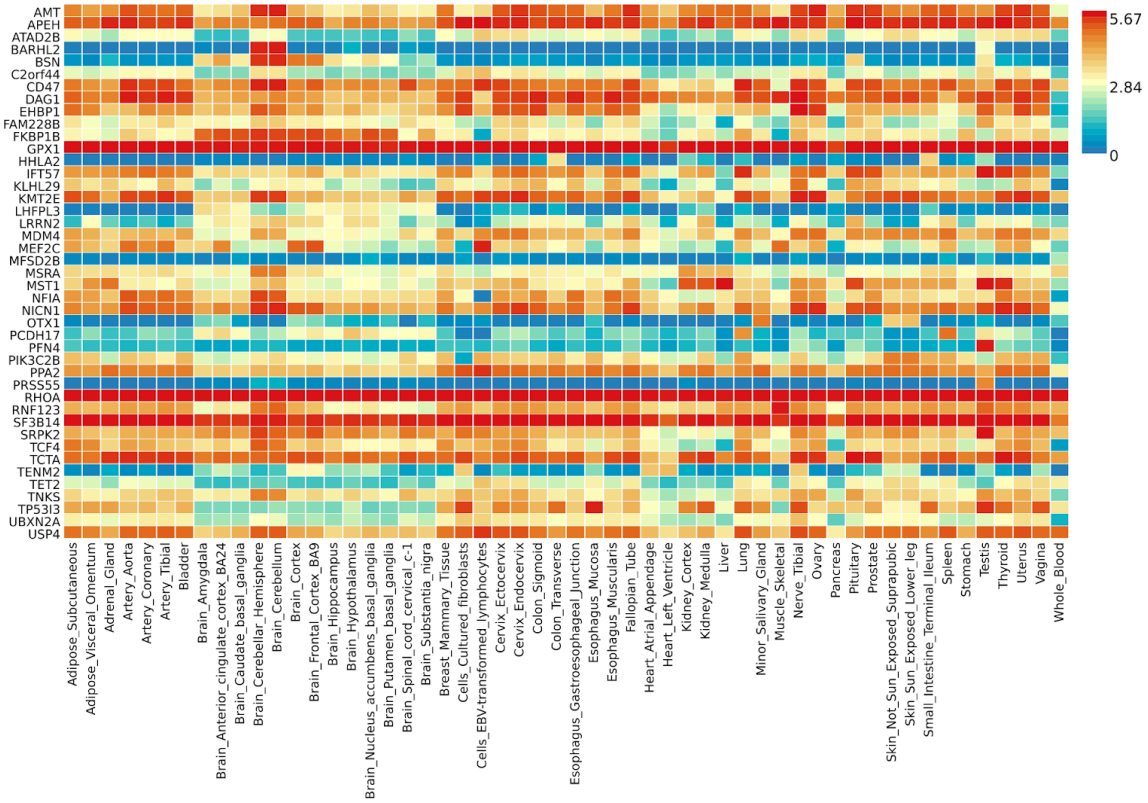
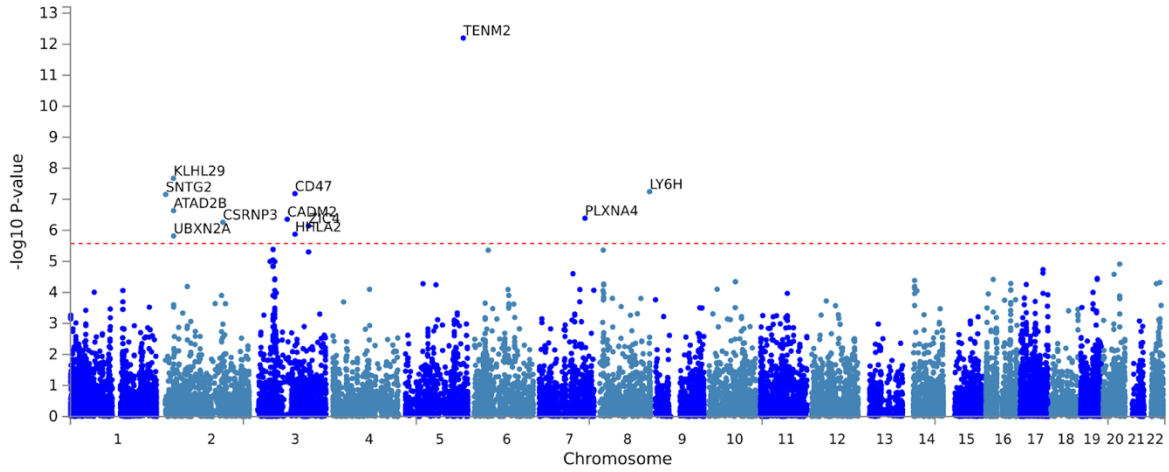


Figure 4.d.3 and Figure 4.d.5 are Manhattan plots of MAGMA gene-based tests of two GWAS of religious attendance without sports/gym or pub/social club. Figure 4.d.4 and Figure 4.d.6 are gene expression heatmaps from positional mapping and enrichment analysis. Out of 45 genes mapped in religious attendance, we identified three genes in all four figures below: CD47, HHLA2, and TENM2; these may play a distinctive role in religious attendance that cannot be explained by the types of social interaction measured by going to sports clubs/gyms or pubs/social clubs. While the CD47 gene encodes a membrane protein with a wide tissue distribution, the HHLA gene encodes a protein-ligand found on the surface of monocytes, and this protein-ligand regulates cell-mediated immunity (Safran et al., 2021;

Stelzer et al., 2016). Gene Ontology (GO) annotations related to the gene TENM2 include calcium ion binding and protein heterodimerization activity (Ashburner et al., 2000; The Gene Ontology Consortium et al., 2021).

Figure 4.d.3 Manhattan plot of "religious-without-sports/gym" GWAS (gene-based test - 12 genes)



Supplementary Section D also includes tissue specificity tests using MAGMA and GWAS results of the common latent factors of religious attendance with sports/gym or pub/social club. The gene expression of religious-without-sports/gym or religious-without-pub/social latent factors in both GWAS-by-subtraction analyses was significant in the brain cerebellar hemispheres and brain cerebellum. GWAS of "religious-without-sports/gym" identified 6 genomic risk loci and "religious-without-pub/social" identified 9 genomic risk loci. The candidate SNPs near the individual significant SNPs are associated with a wide range of health traits in the GWAS catalog, especially blood pressure, BMI, feeling guilty, general risk tolerance, bipolar disorder, and immunity-relevant traits such as hemoglobin levels, red blood cell counts, and platelet count.

Figure 4.d.4 Gene expression heatmap of "religious-without-sports/gym" (6 genes & GTEx v8 54 tissue types)

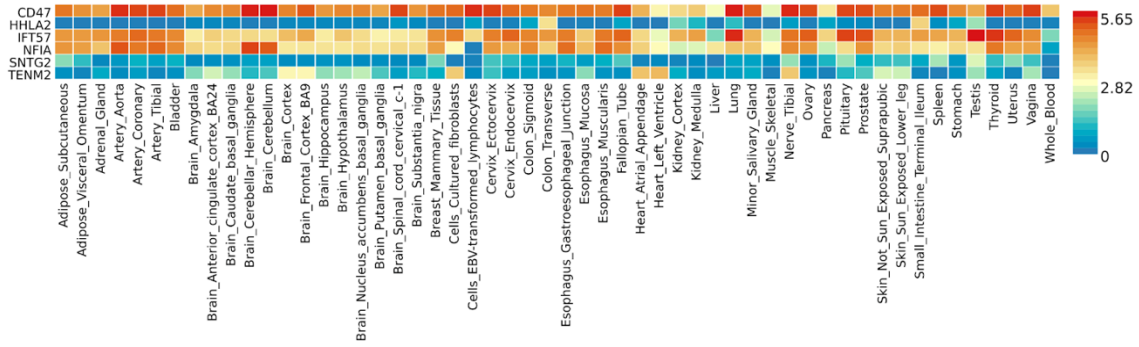


Figure 4.d.5 Manhattan plot of "religious-without-pub/social" GWAS (gene-based test - 17 genes)

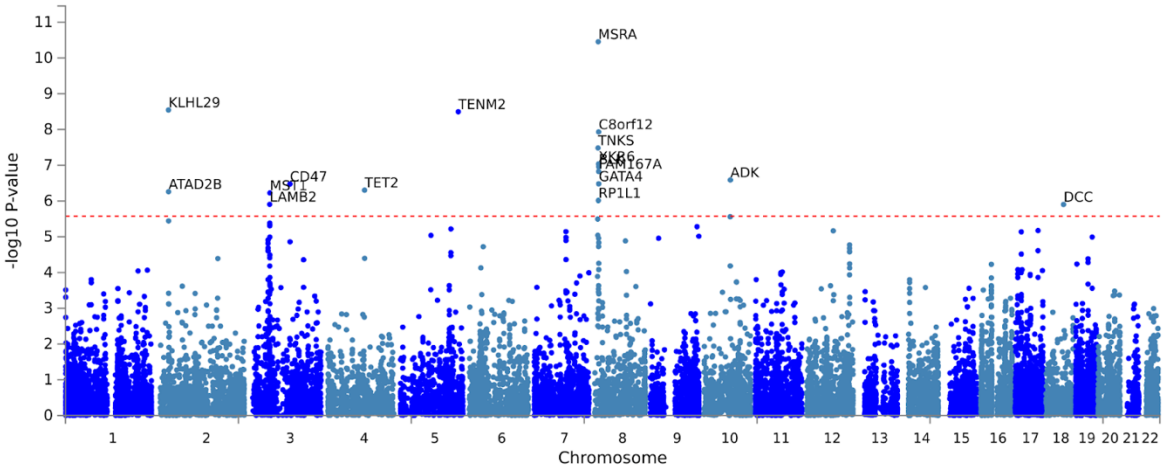
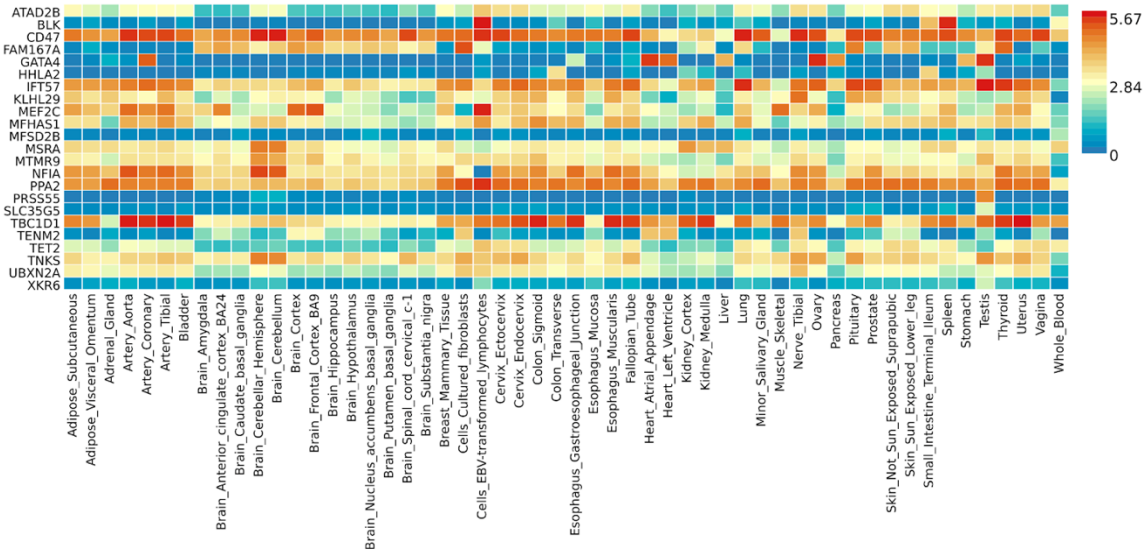


Figure 4.d.6 Gene expression heatmap of "religious-without-pub/social" (24 genes & GTEx v8 54 tissue types)



5. Discussion

In Chapter 1, we utilized GWAS summary statistics and innovative statistical tools to investigate the shared genetic architecture between religious attendance and various demographic traits. Our findings reveal over 300 significant genetic correlations, indicating a negative association between religious attendance and high-risk health behaviors, as well as a positive correlation with better physical and mental health. We replicated the findings in the PGI repository study (Becker et al., 2021) using PGI predictions among three American longitudinal surveys. Our results show that the marginal R^2 of PGI predicting religious attendance in the WLS and HRS data are around 1%, which is similar to the out-of-sample prediction using UK Biobank data. We also find that the prediction is over 1% among the ADH sample, which is a smaller, younger, and less religious sample of American adolescents and young adults. These results suggest that our PGI construction method, using original GWAS summary statistics (Day et al., 2018), is robust and can be used to predict religious attendance in various populations, including younger and less religious samples. Despite a relatively small marginal R^2 of around 1%, the association between PGI and religious attendance is consistently significant across three American longitudinal surveys. Notably, the marginal R^2 of PGI is comparable to commonly included demographic variables, such as birth year and sex. While age and sex have traditionally been considered important predictors in demographic studies, neglecting the potential influence of genetic factors could lead to

incomplete or inaccurate conclusions. To fully understand the underlying causes of demographic traits, it is important for demographers to take genetic factors into account, as they may play an important role in shaping these traits.

The findings from genomic SEM mediation analysis suggest religious attendance has a positive direct genetic effect on the number of everborn children, which is mediated by education and less risky sexual behavior, as seen in the genomic SEM mediation analysis. While some social surveys may not include measures of sensitive variables such as the number of sexual partners, genomic SEM can still be a valuable tool for modeling complex associations among variables that may not be directly measured in the same study. By combining information from multiple sources of GWAS summary statistics data and genetic information, we can obtain a more complete understanding of the genetic factors that contribute to various social and behavioral outcomes. Chapter 2 delves deeper into the relationship between religious attendance and fertility among American older adults by analyzing WLS and HRS data, and it presents similar but distinctive findings.

Additionally, both the two-common factor model and the GWAS-by-subtraction analyses highlight the unique nature of religious attendance. The two-common factor model provides evidence that religious attendance and mental health are separate constructs, characterized by their individual genetic influences and a shared genetic architecture. This highlights the need

for researchers to account for the genetic overlap between these constructs when studying the relationship between religious attendance and mental health. Religious coping strategies, such as prayer and seeking support from a religious community, have also been linked to better mental health outcomes in response to stressful life events (Pargament et al., 2011). However, the relationship between religious attendance and mental health is complex and context-dependent, and some studies have found mixed or even negative associations (Hackney & Sanders, 2003). Additionally, the directionality of the association is not always clear, as some research suggests that better mental health may lead to increased religious involvement rather than the reverse (G. Koenig & Larson, 2001; Smith et al., 2003). We use a quasi-experimental design to further explore the gene-environemnt interaction with respect to religious attendance, adverse life events, and depressive symptoms in Chapter 3.

Similarly, the GWAS-by-subtraction analysis highlights the unique genetic variants associated with religious attendance after accounting for participation in other social activities. This highlights the unique nature of religious attendance and suggests that it cannot simply be reduced to a general social activity or personal characteristic. This finding is in line with the broader sociological and demographic literature, which has long recognized the distinctive role of religion in shaping social and cultural values and practices, such as providing a shared system of values and beliefs that people use to make sense of the world (Stark & Finke, 2000) and fostering social capital by promoting trust and cooperation among

members (Putnam & Campbell, 2012). Moreover, our biological annotations and enrichment analysis, based on GWAS-by-subtraction, suggest that the shared genetic architecture between religious attendance and health has a molecular mechanism possibly through cell immunity.

Overall the findings from this chapter contribute to a more comprehensive understanding of the genetic and environmental factors that shape various social and behavioral outcomes. The strong genetic correlation between religious attendance and other social traits, such as fertility and mental health, underscores the importance of integrating genetic data into demographic studies. Failure to account for genetic confounding can lead to biased estimates and the misattribution of genetic effects to environmental factors. The use of genomic SEM in modeling complex associations among variables, as demonstrated in this study, provides a valuable tool for social scientists to gain a more nuanced understanding of the underlying structure of complex traits such as religious attendance. It highlights the importance of considering not only the direct genetic effects but also the indirect effects of genetic factors through mediating variables. Overall, these findings suggest the importance of integrating genetic data for a better understanding of the genetic factors that contribute to religious attendance and its associations with other social and demographic traits.

The limited availability of large-scale datasets with specific questions on religious attendance restricts the scope of genomic studies on religious attendance. Currently, the UK Biobank dataset is the only large-scale dataset that contains a specific survey question on religious attendance, providing researchers with the opportunity to investigate the shared genetic architecture of religious attendance and other traits. However, the potential selection bias in the UK Biobank dataset raises concerns about the representativeness of the sample, as participants are more likely to be older, female, and living in less socioeconomically deprived areas than the general British population (Fry et al., 2017). This limitation underscores the need for other public datasets to consider adding questions related to religious attendance, which would enable more comprehensive genomic studies of religious attendance

Moreover, the limitations of using LDSC to determine overall genetic correlation are evident in the mediation analysis conducted using genomic SEM, as the lack of significant correlation may be due to the offsetting direct and indirect effects. The genomic SEM assumes specific directions of causality between the variables, which may not fully capture the underlying causal relationships. It is important to acknowledge that the model's goodness of fit is satisfactory, but causal claims cannot be made through these exploratory analyses. The GWAS-by-subtraction analysis also uses a strong assumption of zero correlation between two latent factors, which may be violated. To further examine the thought experiment and insights drawn from the exploratory analyses, new evidence is necessary. Future PGI construction and

genetic correlation analyses could be performed on latent factors derived from GWAS-by-subtraction to compare with the results presented in this chapter. Further development of genomic SEM is needed to integrate more than two GWAS results for GWAS-by-subtraction analysis. To better understand the genetic variants associated with religious attendance, a more comprehensive approach could be taken by integrating all three variables (religious attendance, attending sports clubs/gyms, and attending pubs/social clubs) into a single model, rather than conducting GWAS-by-subtraction with each variable separately. This could reveal the unique genetic variants associated with religious attendance after accounting for participation in both sports clubs/gyms and pubs/social clubs simultaneously. The availability of GWAS summary statistics and advancements in statistical genetics tools will make future investigations into the genetics of religiosity more informative.

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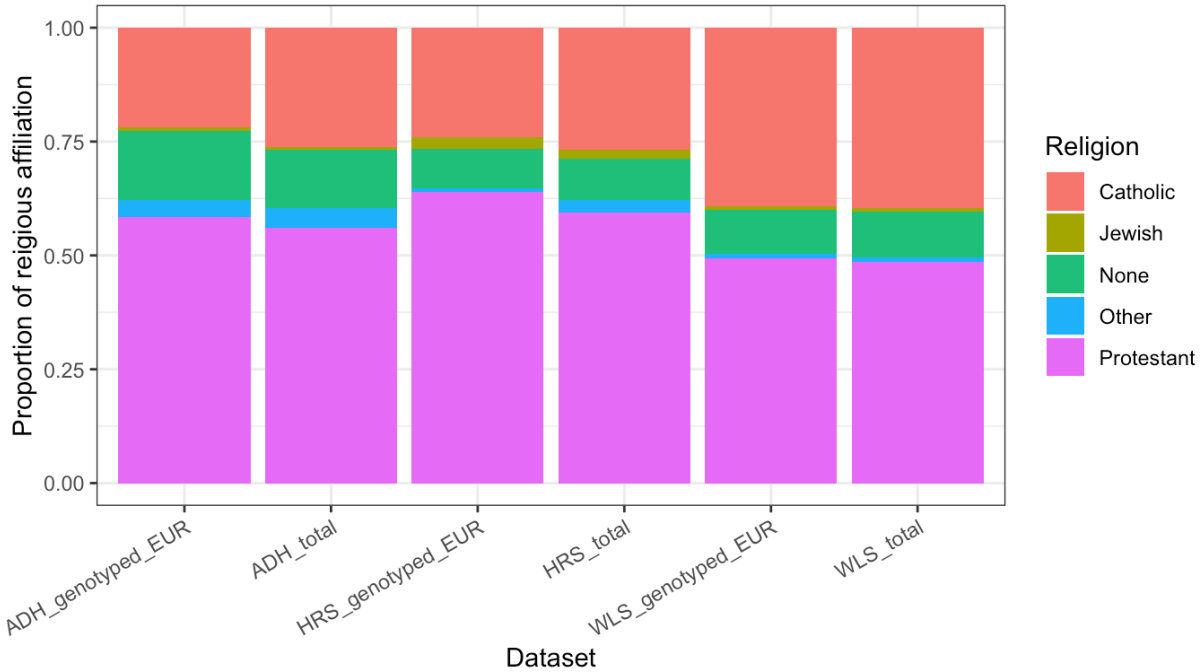
Chapter 1 Supplementary Materials

A. Measure Religiosity

a. Religious affiliation

There are three types of commonly asked questions in the three surveys (WLS, HRS, and ADH) related to religiosity: religious preference/affiliation, religious attendance, and the importance of religion to respondents. WLS (Herd et al., 2014) has the largest proportion of Catholics, and HRS (The University of Michigan, 2020) has the largest proportion of protestants, while ADH (Harris, Kathleen Mullan, 2018) as the least religious sample, has the largest proportion of individuals with no religious affiliation or other religions. Generally, there is a larger proportion of Protestants and non-affiliated individuals in the genotyped samples from individuals of European ancestry compared to the entire sample across all three datasets.

Figure A.a.1 The proportion of religious affiliation among all and genotyped non-Hispanic European samples

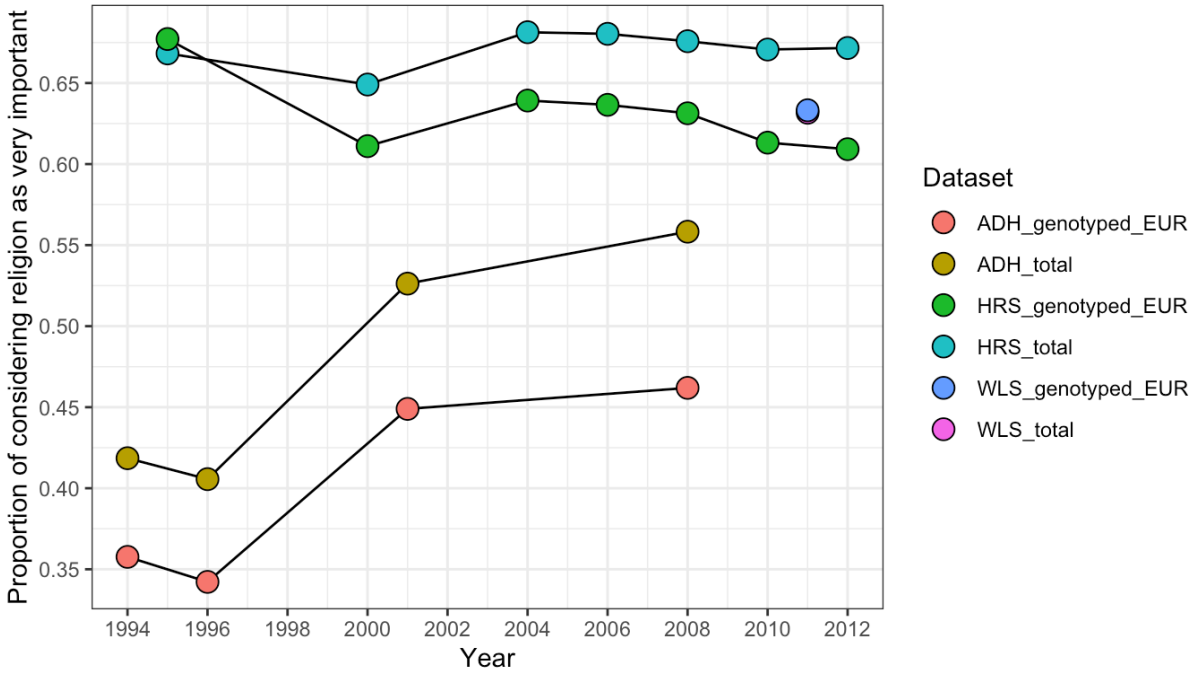


b. Religious importance

WLS only has one wave asking the question of how important religion is, and the proportion of respondents answering very important was around 63% for both the total and the genotyped European sample. Similarly, more than 60% of HRS respondents said religion was very important to them, but the genotyped sample had lower importance ratings than the total sample. ADH sample has the lowest importance ratings, with only around 20% of respondents saying that religion was very important to them. However, there was a significant change in the proportion of respondents who answered that religion was very important to them after the first two waves, likely due to a different framing of the answers. In the third and fourth waves, the options were “not important, somewhat important, very important, more important than anything else," resulting in a larger proportion of respondents indicating that religion was important to them.

Despite the lower importance ratings in the ADH sample, especially the genotyped European sample, the scale for the third and fourth waves was still over 40%, suggesting that religion remains an important aspect of life for a substantial proportion of individuals in this sample. The increasing trend from 2001 to 2008 may also indicate that the importance of religion could increase among more religious respondents as they age.

Figure A.b.2 The proportion of respondents considering religion as very important among all and genotyped non-Hispanic European samples



B. PGI construction and prediction

To make PGI results more comparable across different datasets and phenotypes, the PGI repository (Becker et al., 2021) standardized the PGI construction. This paper used their data processing methods and PRSice2 (Choi & O'Reilly, 2019) to construct PGIs. The reproduced PGI for WLS is 0.67% and for HRS is 0.85%. Both are lower than the best predictions using other methods presented in Table B.1.

The religious attendance evaluated in the UKBiobank discovery dataset (Day et al., 2018) is binary on whether a respondent attends religious group activities once a week or more. However, the PGI repository used categorical variables in the HRS and WLS as numerical values to be predicted. Table B.1 has four coding strategies for aggregating religious attendance across the waves. Binary coding [strict] means only those who answered attending religious activities at least weekly in every wave reported were coded as 1. Binary coding [more than half] means those who answered attending religious activities at least weekly in more than half of the waves reported were coded as 1, while the Binary coding [half] relaxed the criteria a bit more by including those who reported weekly religious attendance half of the times. For instance, for a WLS respondent who reported religious attendance for four waves, she will be coded as 1 only if she attended religious activities for all four waves under strict binary coding, while three out of four waves are needed for "more-than-half" binary coding, and only two waves of reporting weekly attendance will qualify her as being religious in "including-half" binary coding. The continuous coding transformed the categorical variables into numeric variables by estimating the total number of attending religious activities per year for each wave and used the mean value scaled to range from 0 to 1 as the aggregated continuous phenotype.

PGI repository did not use the same birth year for each individual with multi-wave data, but instead, the religious attendance was residualized on a second-degree polynomial for age, sex, and the interaction of age and sex for that specific wave, and the mean of the residualized values across waves was used as the aggregated continuous phenotype. Compared to using waves only from 2004 to 2016, more waves from 1992 to 2018 were used to construct HRS PGI. Four different sets of covariates were tested, shown in Table B.1. Only birth year across waves was used as a covariate instead of changing ages in different waves. "Second_degree" means adding a second-degree polynomial for birth year and the interaction of birth year and sex to the third set of covariates with age, sex, their interactions, and the top 10 PCs.

Full R^2 is the variance explained by the full model, including the covariates. Binary [more than half] coding has the highest PGI prediction, and adding second-degree polynomials works the best for HRS data as HRS has a wider range of birth cohorts. The efforts for standardizing PGI construction are useful for better comparison across datasets and phenotypes. However, Table B.1 illustrates that different methods of aggregating phenotypes across waves from the longitudinal study could affect PGI construction and predictability. For example, the difference in variance explained by PGI using different coding strategies in ADH is more than 0.4%.

Table B.1 Variance explained by PGI and the full model including PGI and covariates

Different coding strategies		**WLS**		**HRS**		**ADH**	
Binary/ Continuous	**Covariates**	**PGI R^2 (%)**	**Full R^2 (%)**	**PGI R^2 (%)**	**Full R^2 (%)**	**PGI R^2 (%)**	**Full R^2 (%)**
Binary Coding [strict]	None	0.66	0.66	0.92	0.92	1.40	1.40
	Byear * sex	0.63	4.03	0.88	2.59	1.46	2.16
	Byear * sex + PCs	0.79	5.27	0.93	3.85	1.43	3.43
	Second_degree	0.78	5.40	0.95	4.01	1.43	3.44
Binary Coding [more than half]	None	0.77	0.77	0.97	0.97	1.45	1.45
	Byear * sex	0.75	4.85	0.97	6.17	1.45	2.08
	Byear * sex + PCs	**0.85**	5.74	0.98	8.08	**1.51**	3.93
	Second_degree	0.84	5.91	**1.00**	8.54	1.50	3.97
Binary Coding [including half]	None	0.73	0.73	0.76	0.76	1.10	1.10
	Byear * sex	0.72	4.51	0.76	6.33	1.05	3.04
	Byear * sex + PCs	0.83	5.18	0.80	8.30	1.10	4.44
	Second_degree	0.82	5.29	0.81	8.61	1.11	4.51
Continuous Coding	None	0.69	0.69	0.82	0.82	1.27	1.27
	Byear * sex	0.67	3.30	0.82	4.81	1.24	2.39
	Byear * sex + PCs	0.73	3.68	0.80	6.26	1.29	3.76
	Second_degree	0.72	3.71	0.81	6.53	1.28	3.76

C. Genetic Correlation

a. Overall Genetic Correlation

Table C.a.1 Overall genetic correlation between religious attendance and other traits

Note: CVD is the acronym for Cardiovascular Diseases and SES denotes Socio-economic Status

Category	Datafields	Trait	rG	p(rG)
Alcohol	20117_2	Alcohol drinker status: Current	0.2297	1.23E-06
Alcohol	20403	Amount of alcohol drunk on a typical drinking day	-0.2598	1.63E-08
Alcohol	2664_3	Reason for reducing amount of alcohol drunk: Health precaution	0.2812	6.48E-10
Alcohol	20414	Frequency of drinking alcohol	0.2408	5.07E-11
Alcohol	1588	Average weekly beer plus cider intake	-0.3748	2.45E-12
Alcohol	1558	Alcohol intake frequency.	-0.3019	2.77E-24
Alcohol	1568	Average weekly red wine intake	0.4828	2.53E-36
Alcohol	1628	Alcohol intake versus 10 years previously	-0.4991	7.48E-44
Alcohol	1618	Alcohol usually taken with meals	0.5097	1.57E-49
Alcohol	20117_1	Alcohol drinker status: Previous	-0.3506	6.42E-12
Alcohol	1578	Average weekly champagne plus white wine intake	0.3502	4.43E-19
Anthropometry	23104	Body mass index (BMI)	-0.2504	8.69E-24
Anthropometry	20015	Sitting height	0.08787	2.28E-05
Anthropometry	50	Standing height	0.1154	5.95E-09
Anthropometry	3143	Ankle spacing width	-0.1121	3.35E-05
Anthropometry	23126	Arm predicted mass (left)	-0.1074	1.39E-06
Anthropometry	23125	Arm fat-free mass (left)	-0.1065	1.39E-06
Anthropometry	23109	Impedance of arm (right)	0.1439	1.09E-09
Anthropometry	23110	Impedance of arm (left)	0.1605	1.84E-12
Anthropometry	23112	Leg fat mass (right)	-0.2648	1.37E-27
Anthropometry	23116	Leg fat mass (left)	-0.2659	6.55E-28
Anthropometry	23111	Leg fat percentage (right)	-0.3135	7.24E-41
Anthropometry	23115	Leg fat percentage (left)	-0.3173	4.08E-42

Anthropometry	23124	Arm fat mass (left)	-0.2192	1.76E-18
Anthropometry	23123	Arm fat percentage (left)	-0.2233	8.32E-19
Anthropometry	23120	Arm fat mass (right)	-0.2238	4.98E-19
Anthropometry	23119	Arm fat percentage (right)	-0.2328	1.08E-20
Anthropometry	23127	Trunk fat percentage	-0.23	2.82E-22
Anthropometry	2744	Birth weight of first child	0.17	4.74E-06
Anthropometry	49	Hip circumference	-0.1342	7.30E-08
Anthropometry	20536_0	Weight change during worst episode of depression: Stayed about the same or was on a diet	0.3583	5.59E-08
Anthropometry	2306	Weight change compared with 1 year ago	-0.3924	4.15E-09
Anthropometry	21002	Weight	-0.161	1.25E-11
Anthropometry	23098	Weight	-0.1621	7.93E-12
Anthropometry	48	Waist circumference	-0.2272	2.87E-20
Anthropometry	23100	Whole body fat mass	-0.2329	1.36E-21
Anthropometry	23099	Body fat percentage	-0.2601	8.24E-28
Anthropometry	23128	Trunk fat mass	-0.2111	1.84E-18
Childhood	20487	Felt hated by family member as a child	-0.2182	2.52E-06
Childhood	20491	Someone to take to doctor when needed as a child	0.5273	3.38E-17
Childhood	20489	Felt loved as a child	0.342	1.49E-18
Childhood	1677	Breastfed as a baby	0.4563	1.09E-20
CVD	I25	Diagnoses - main ICD10: I25 Chronic ischaemic heart disease	-0.1605	3.66E-05
CVD	6153_2	Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones: Blood pressure medication	-0.1649	7.54E-06
CVD	6177_100	Medication for cholesterol, blood pressure or diabetes: None of the above	0.1642	2.47E-06
CVD	6177_2	Medication for cholesterol, blood pressure or diabetes: Blood pressure medication	-0.1729	1.49E-06
CVD	I9_IHD	Ischaemic heart disease, wide definition	-0.1721	5.68E-07
CVD	4080	Systolic blood pressure, automated reading	-0.1617	2.40E-08
CVD	4079	Diastolic blood pressure, automated reading	-0.1722	2.30E-09
CVD	6150_4	Vascular/heart problems diagnosed by doctor: High blood pressure	-0.1899	2.44E-10

CVD	20002_1065	Non-cancer illness code, self-reported: hypertension	-0.1896	2.37E-10
CVD	6150_100	Vascular/heart problems diagnosed by doctor: None of the above	0.2123	3.37E-13
CVD	21021	Pulse wave Arterial Stiffness index	-0.2236	4.58E-05
CVD	30020	Haemoglobin concentration	-0.1071	5.19E-06
CVD	6150_1	Vascular/heart problems diagnosed by doctor: Heart attack	-0.2069	1.48E-06
Diabetes	20002_1220	Non-cancer illness code, self-reported: diabetes	-0.1934	6.40E-08
Diabetes	2443	Diabetes diagnosed by doctor	-0.1857	4.41E-08
Diet	6144_1	Never eat eggs, dairy, wheat, sugar: Eggs or foods containing eggs	-0.2953	5.35E-06
Diet	100011	Iron	0.4168	1.13E-06
Diet	1309	Fresh fruit intake	0.1825	1.23E-07
Diet	1438	Bread intake	0.1475	5.38E-08
Diet	1359	Poultry intake	-0.2426	3.07E-10
Diet	2654_4	Non-butter spread type details: Soft (tub) margarine	-0.4509	1.81E-16
Diet	1478	Salt added to food	-0.2726	2.77E-21
Diet	6144_5	Never eat eggs, dairy, wheat, sugar: I eat all of the above	0.3772	1.11E-25
Diet	1468_5	Cereal type: Other (e.g. Cornflakes, Frosties)	-0.3999	7.24E-26
Diet	1458	Cereal intake	0.3476	1.24E-34
Diet	1448_1	Bread type: White	-0.4752	2.94E-38
Diet	1319	Dried fruit intake	0.4057	4.79E-40
Diet	1448_3	Bread type: Wholemeal or wholegrain	0.5178	6.70E-46
Diet	1468_4	Cereal type: Muesli	0.5075	8.96E-56
Diet	1408	Cheese intake	0.5127	4.44E-68
Diet	100016	Potassium	0.2987	4.04E-05
Diet	1538_0	Major dietary changes in the last 5 years: No	0.1683	4.56E-06
Diet	100017	Magnesium	0.3815	1.06E-07
Diet	1548	Variation in diet	-0.1885	6.21E-08
Diet	6179_2	Mineral and other dietary supplements: Glucosamine	0.2441	2.74E-09

Diet	1498	Coffee intake	0.229	7.33E-11
Diet	1508_3	Coffee type: Ground coffee (include espresso, filter etc)	0.3671	5.80E-30
Diet	1508_2	Coffee type: Instant coffee	-0.4345	9.29E-20
Diet	6144_4	Never eat eggs, dairy, wheat, sugar: Sugar or foods/drinks containing sugar	-0.3389	3.73E-21
Diet	110001	Invitation to complete online 24-hour recall dietary questionnaire, acceptance	0.4054	3.81E-27
Diet	20077	Number of diet questionnaires completed	0.3563	2.01E-14
Diet	1538_1	Major dietary changes in the last 5 years: Yes, because of illness	-0.2633	5.15E-11
Disability	2188	Long-standing illness, disability or infirmity	-0.1997	4.58E-10
Disability	6146_3	Attendance/disability/mobility allowance: Blue badge	-0.3949	1.79E-19
Disability	6142_4	Current employment status: Unable to work because of sickness or disability	-0.5048	9.72E-31
Disability	6146_100	Attendance/disability/mobility allowance: None of the above	0.4532	8.00E-31
Disability	6146_2	Attendance/disability/mobility allowance: Disability living allowance	-0.4747	6.30E-33
Exercise	864	Number of days/week walked 10+ minutes	-0.1649	2.90E-06
Exercise	6164_3	Types of physical activity in last 4 weeks: Strenuous sports	0.3268	1.57E-14
Exercise	6164_5	Types of physical activity in last 4 weeks: Heavy DIY (eg: weeding, lawn mowing, carpentry, digging)	0.2812	3.96E-15
Exercise	894	Duration of moderate activity	-0.4233	4.34E-28
Exercise	6164_2	Types of physical activity in last 4 weeks: Other exercises (eg: swimming, cycling, keep fit, bowling)	0.3786	6.96E-29
Exercise	6164_100	Types of physical activity in last 4 weeks: None of the above	-0.4671	4.79E-29
Exercise	874	Duration of walks	-0.3827	2.73E-30
Exercise	6164_4	Types of physical activity in last 4 weeks: Light DIY (eg: pruning, watering the lawn)	0.4269	1.96E-35
Exercise	6164_1	Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport)	0.4945	1.02E-55
Exercise	914	Duration of vigorous activity	-0.3544	3.16E-16
Exercise	943	Frequency of stair climbing in last 4 weeks	0.3081	1.56E-18
Exercise	971	Frequency of walking for pleasure in last 4 weeks	-0.3647	9.70E-19
Exercise	924	Usual walking pace	0.3465	1.19E-35
Exercise	6032	Maximum workload during fitness test	0.2772	3.75E-05
Finance	728	Number of vehicles in household	0.227	9.54E-11

Finance	4581	Financial situation satisfaction	0.3804	1.38E-16
Finance	680_1	Own or rent accommodation lived in: Own outright (by you or someone in your household)	0.4855	9.38E-49
Finance	680_3	Own or rent accommodation lived in: Rent - from local authority, local council, housing association	-0.6126	6.31E-70
Finance	738	Average total household income before tax	0.5425	5.06E-98
Health	102	Pulse rate, automated reading	-0.112	3.32E-06
Health	N39	Diagnoses - main ICD10: N39 Other disorders of urinary system	-0.238	4.03E-05
Health	20002_1075	Non-cancer illness code, self-reported: heart attack/myocardial infarction	-0.1913	1.07E-05
Health	G6_CARPTU	Carpal tunnel syndrome	-0.1948	3.01E-06
Health	6145_100	Illness, injury, bereavement, stress in last 2 years: None of the above	0.2193	4.57E-07
Health	M13_ARTHROSIS	Arthrosis	-0.2313	4.15E-07
Health	M13_OTHERJOINT	Other joint disorders	-0.2455	2.01E-07
Health	20002_1465	Non-cancer illness code, self-reported: osteoarthritis	-0.2323	1.80E-07
Health	6150_2	Vascular/heart problems diagnosed by doctor: Angina	-0.2299	9.46E-08
Health	135	Number of self-reported non-cancer illnesses	-0.1777	6.25E-09
Health	4548	Health satisfaction	0.2624	9.08E-11
Health	IX_CIRCULATORY	Diseases of the circulatory system	-0.2645	6.12E-12
Health	2178	Overall health rating	-0.4175	1.45E-58
Health	20002_1138	Non-cancer illness code, self-reported: gastro-oesophageal reflux (gord) / gastric reflux	-0.26	1.78E-06
Health	K44	Diagnoses - main ICD10: K44 Diaphragmatic hernia	-0.3474	5.01E-07
Health	20002_1074	Non-cancer illness code, self-reported: angina	-0.2237	9.74E-08
Health	G56	Diagnoses - main ICD10: G56 Mononeuropathies of upper limb	-0.2237	3.03E-08
Health	M13_LOWBACKPAIN	Low back pain	-0.345	1.34E-08
Health	6152_9	Blood clot, DVT, bronchitis, emphysema, asthma, rhinitis, eczema, allergy diagnosed by doctor: Hayfever, allergic rhinitis or eczema	0.1626	1.17E-09
Health	R10	Diagnoses - main ICD10: R10 Abdominal and pelvic pain	-0.3572	5.49E-11
Health	K11_HERNIA	Hernia	-0.1877	2.75E-05
Health	20002_1474	Non-cancer illness code, self-reported: hiatus hernia	-0.2611	8.95E-06
Health	30030	Haematocrit percentage	-0.1085	7.46E-06

Health	3591	Ever had hysterectomy (womb removed)	-0.2511	5.81E-06
Health	6152_6	Blood clot, DVT, bronchitis, emphysema, asthma, rhinitis, eczema, allergy diagnosed by doctor: Emphysema/chronic bronchitis	-0.3334	1.48E-08
Health	30240	Reticulocyte percentage	-0.1536	6.94E-09
Health	6147_1	Reason for glasses/contact lenses: For short-sightedness, i.e. only or mainly for distance viewing such as driving, cinema etc (called 'myopia')	0.2515	1.71E-09
Health	3536	Age started hormone-replacement therapy (HRT)	0.3338	8.09E-10
Health	20459	General happiness with own health	-0.267	4.84E-10
Health	2207	Wears glasses or contact lenses	0.3153	1.74E-10
Health	XIX_INJURY_POISON	Injury, poisoning and certain other consequences of external causes	-0.3093	1.46E-10
Health	KNEE_ARTHROSIS	Gonarthrosis [arthrosis of knee](FG)	-0.2805	8.38E-11
Health	M17	Diagnoses - main ICD10: M17 Gonarthrosis [arthrosis of knee]	-0.2805	8.38E-11
Health	20511	Recent poor appetite or overeating	-0.3353	2.50E-11
Health	VI_NERVOUS	Diseases of the nervous system	-0.31	2.02E-11
Health	G6_NERPLEX	Nerve, nerve root and plexus disorders	-0.2687	1.92E-11
Health	M54	Diagnoses - main ICD10: M54 Dorsalgia	-0.3689	5.80E-12
Health	20107_6	Illnesses of father: Chronic bronchitis/emphysema	-0.3906	4.76E-12
Health	PULMONARYDG	Other pulmonary diagnosis	-0.4001	1.85E-12
Health	20107_3	Illnesses of father: Lung cancer	-0.3673	8.03E-13
Health	COPD_EXCL	COPD differential diagnosis	-0.4113	6.51E-14
Health	6149_100	Mouth/teeth dental problems: None of the above	0.3816	9.51E-31
Health	6149_6	Mouth/teeth dental problems: Dentures	-0.4385	1.56E-47
Health	XI_DIGESTIVE	Diseases of the digestive system	-0.3057	1.72E-15
Health	30510	Creatinine (enzymatic) in urine	-0.2622	4.75E-16
Health	6147_4	Reason for glasses/contact lenses: For 'astigmatism'	0.5906	4.81E-17
Health	2814	Ever used hormone-replacement therapy (HRT)	-0.3373	3.73E-17
Health	R07	Diagnoses - main ICD10: R07 Pain in throat and chest	-0.3654	2.67E-17
Health	XIV_GENITOURINARY	Diseases of the genitourinary system	-0.3235	6.20E-15
Health	XIII_MUSCULOSKELET	Diseases of the musculoskeletal system and connective tissue	-0.3143	3.40E-15

Health	30000	White blood cell (leukocyte) count	-0.2231	1.69E-17
Health	30530	Sodium in urine	-0.3051	6.74E-20
Health	XVIII_MISCFINDINGS	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	-0.3629	8.77E-24
Health	2217	Age started wearing glasses or contact lenses	-0.3504	1.83E-35
Health	2385	Relative age voice broke	0.1651	4.92E-05
Health	30250	Reticulocyte count	-0.1591	6.38E-10
Health	4717	Shortness of breath walking on level ground	-0.3099	2.06E-11
Health	30140	Neutrophill count	-0.1969	1.14E-11
Health	30120	Lymphocyte count	-0.1816	1.41E-13
Health	6149_4	Mouth/teeth dental problems: Loose teeth	-0.4332	5.89E-14
Health	30130	Monocyte count	-0.1044	3.88E-05
Health	4836	Loud music exposure frequency	-0.2597	1.99E-06
Health	20153	Forced expiratory volume in 1-second (FEV1), predicted	0.12	1.57E-06
Health	4270	Volume level set by participant (left)	-0.3346	5.31E-07
Health	3064	Peak expiratory flow (PEF)	0.1955	5.88E-10
Health	30290	High light scatter reticulocyte percentage	-0.1722	2.57E-11
Health	20154	Forced expiratory volume in 1-second (FEV1), predicted percentage	0.2012	1.92E-11
Health	30300	High light scatter reticulocyte count	-0.1766	2.66E-12
Health	41231_1	Hospital episode type: General episode	-0.3471	4.15E-13
Health	3062	Forced vital capacity (FVC)	0.189	2.81E-15
Health	3063	Forced expiratory volume in 1-second (FEV1)	0.206	2.12E-16
Health	20151	Forced vital capacity (FVC), Best measure	0.1941	1.96E-16
Health	41235	Spells in hospital	-0.3614	2.45E-18
Health	2316	Wheeze or whistling in the chest in last year	-0.3238	6.75E-21
Health	2277	Frequency of solarium/sunlamp use	-0.4441	2.66E-27
Health	30280	Immature reticulocyte fraction	-0.175	2.85E-11
Health	20150	Forced expiratory volume in 1-second (FEV1), Best measure	0.2085	9.37E-17

Health of relatives	20111_8	Illnesses of siblings: High blood pressure	-0.1459	4.41E-05
Health of relatives	20107_1	Illnesses of father: Heart disease	0.1707	1.39E-06
Health of relatives	20111_9	Illnesses of siblings: Diabetes	-0.2424	2.60E-07
Health of relatives	1807	Father's age at death	0.4345	3.86E-20
Health of relatives	3526	Mother's age at death	0.5523	2.34E-21
Health of relatives	20110_9	Illnesses of mother: Diabetes	-0.2214	5.08E-08
Health of relatives	20111_1	Illnesses of siblings: Heart disease	-0.2817	1.47E-08
Health of relatives	20111_100	Illnesses of siblings: None of the above (group 1)	0.2644	2.51E-13
Health of relatives	20110_6	Illnesses of mother: Chronic bronchitis/emphysema	-0.3762	8.01E-12
Intelligence	20016	Fluid intelligence score	0.4699	2.66E-61
Intelligence	20128	Number of fluid intelligence questions attempted within time limit	0.2481	6.68E-11
Intelligence	5001	FI7 : synonym	0.4703	1.08E-18
Intelligence	4979	FI5 : family relationship calculation	0.4807	1.27E-19
Intelligence	5012	FI8 : chained arithmetic	0.4117	1.24E-24
Intelligence	4957	FI3 : word interpolation	0.4726	2.82E-31
Intelligence	4968	FI4 : positional arithmetic	0.5244	4.27E-37
Intelligence	5556	FI9 : concept interpolation	0.6781	1.46E-39
Intelligence	4990	FI6 : conditional arithmetic	0.5284	2.85E-45
Intelligence	20018	Prospective memory result	-0.4237	2.11E-22
Medication	6154_1	Medication for pain relief, constipation, heartburn: Aspirin	-0.1903	1.38E-05
Medication	20003_1140868226	Treatment/medication code: aspirin	-0.1895	1.29E-05
Medication	20003_1140884600	Treatment/medication code: metformin	-0.1834	2.57E-06
Medication	20003_1140860806	Treatment/medication code: ramipril	-0.2331	7.97E-07
Medication	6153_1	Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones: Cholesterol lowering medication	-0.2022	7.13E-07
Medication	20003_1140864752	Treatment/medication code: lansoprazole	-0.2934	9.70E-08
Medication	6154_3	Medication for pain relief, constipation, heartburn: Paracetamol	-0.2037	1.29E-08
Medication	6154_5	Medication for pain relief, constipation, heartburn: Omeprazole (e.g. Zanprol)	-0.2906	3.74E-10

Medication	2492	Taking other prescription medications	-0.2041	3.65E-11
Medication	20003_1141194794	Treatment/medication code: bendroflumethiazide	-0.2121	2.87E-06
Medication	20003_2038460150	Treatment/medication code: paracetamol	-0.211	4.14E-08
Medication	6154_100	Medication for pain relief, constipation, heartburn: None of the above	0.2592	6.57E-17
Medication	6153_100	Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones: None of the above	0.2501	1.83E-11
Medication	20003_1140865634	Treatment/medication code: omeprazole	-0.359	1.03E-12
Medication	137	Number of treatments/medications taken	-0.2233	1.65E-13
Medication	20003_1140923346	Treatment/medication code: co-codamol	-0.4242	9.25E-15
Pain	6154_2	Medication for pain relief, constipation, heartburn: Ibuprofen (e.g. Nurofen)	-0.1791	4.74E-05
Pain	2335	Chest pain or discomfort	-0.1879	5.87E-07
Pain	6159_8	Pain type(s) experienced in last month: Pain all over the body	-0.3693	2.87E-09
Pain	6159_4	Pain type(s) experienced in last month: Back pain	-0.2914	4.15E-18
Pain	6159_100	Pain type(s) experienced in last month: None of the above	0.3503	3.20E-32
Pain	6159_7	Pain type(s) experienced in last month: Knee pain	-0.3311	2.19E-24
Pain	4728	Leg pain on walking	-0.4013	1.76E-15
Pain	3606	Chest pain or discomfort walking normally	-0.4653	3.07E-17
Pain	6159_3	Pain type(s) experienced in last month: Neck or shoulder pain	-0.333	9.94E-19
Pain	6159_6	Pain type(s) experienced in last month: Hip pain	-0.3199	3.64E-15
Pain	M13_DORSALGIA	Dorsalgia	-0.3689	5.80E-12
Psychiatric	2040	Risk taking	-0.1719	3.96E-07
Psychiatric	20510	Recent feelings of depression	-0.2046	3.63E-05
Psychiatric	20505	Recent easy annoyance or irritability	-0.2402	1.19E-05
Psychiatric	1920	Mood swings	-0.2269	4.74E-08
Psychiatric	20519	Recent feelings of tiredness or low energy	-0.2498	4.15E-08
Psychiatric	1200	Sleeplessness / insomnia	-0.1987	6.36E-09
Psychiatric	2080	Frequency of tiredness / lethargy in last 2 weeks	-0.2016	1.48E-09
Psychiatric	2000	Worry too long after embarrassment	0.2199	6.46E-11

Psychiatric	2020	Loneliness, isolation	-0.2934	6.84E-14
Psychiatric	2060	Frequency of unenthusiasm / disinterest in last 2 weeks	-0.3958	3.53E-21
Psychiatric	2110	Able to confide	0.3056	1.14E-22
Psychiatric	2070	Frequency of tenseness / restlessness in last 2 weeks	-0.2179	8.80E-09
Psychiatric	1960	Fed-up feelings	-0.3156	8.85E-14
Psychiatric	20517	Trouble falling or staying asleep, or sleeping too much	-0.217	1.90E-05
Psychiatric	4653	Ever highly irritable/argumentative for 2 days	-0.28	1.15E-07
Psychiatric	20514	Recent lack of interest or pleasure in doing things	-0.3342	3.35E-10
Reproduction	3581	Age at menopause (last menstrual period)	0.164	1.16E-06
Reproduction	20522	Been in a confiding relationship as an adult	0.4259	1.17E-13
Reproduction	3849	Number of pregnancy terminations	-0.5274	1.67E-16
Reproduction	2794	Age started oral contraceptive pill	0.493	3.35E-38
Reproduction	2149	Lifetime number of sexual partners	-0.3966	3.11E-43
Reproduction	2764	Age at last live birth	0.4888	3.73E-51
Reproduction	2754	Age at first live birth	0.5524	2.25E-100
Reproduction	2139	Age first had sexual intercourse	0.6446	2.50E-255
Reproduction	2129	Answered sexual history questions	-0.2878	2.00E-14
SES	6138_4	Qualifications: CSEs or equivalent	-0.4	4.67E-19
SES	6138_5	Qualifications: NVQ or HND or HNC or equivalent	-0.4862	5.56E-20
SES	6138_3	Qualifications: O levels/GCSEs or equivalent	0.6692	3.76E-99
SES	22501	Year ended full time education	0.6552	3.48E-116
SES	845	Age completed full time education	0.6289	1.70E-138
SES	6138_2	Qualifications: A levels/AS levels or equivalent	0.6713	1.45E-184
SES	6138_6	Qualifications: Other professional qualifications eg: nursing, teaching	0.7972	3.20E-186
SES	6138_100	Qualifications: None of the above	-0.682	1.04E-224
SES	6138_1	Qualifications: College or University degree	0.6481	6.67E-242
SES	6142_1	Current employment status: In paid employment or self-employed	0.3186	1.42E-10

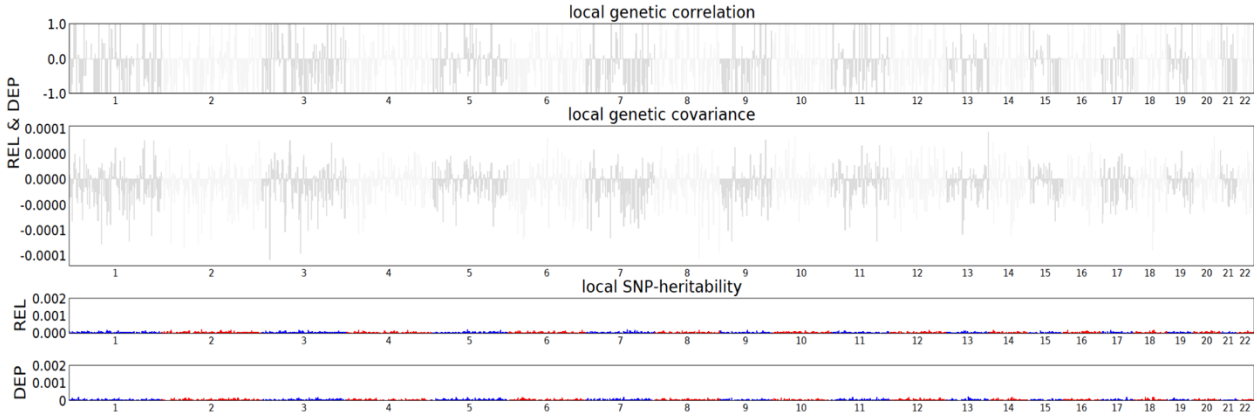
SES	22617_2314	Job SOC coding: Secondary education teaching professionals	0.5018	6.48E-12
SES	22601_23143401	Job coding: secondary school teacher or teaching professional (including head teacher)	0.5116	3.33E-12
SES	826	Job involves shift work	-0.5205	1.01E-26
SES	806	Job involves mainly walking or standing	-0.5753	4.42E-66
SES	816	Job involves heavy manual or physical work	-0.5992	1.68E-81
SES	189	Townsend deprivation index at recruitment	-0.4583	6.48E-39
SES	670_1	Type of accommodation lived in: A house or bungalow	0.3412	8.66E-13
SES	6145_6	Illness, injury, bereavement, stress in last 2 years: Financial difficulties	-0.3066	4.46E-17
Sibling	1883	Number of full sisters	-0.2514	1.32E-06
Sibling	1873	Number of full brothers	-0.27	6.28E-08
Smoking	2887	Number of cigarettes previously smoked daily	-0.1979	1.47E-05
Smoking	20116_1	Smoking status: Previous	-0.1922	1.63E-09
Smoking	20160	Ever smoked	-0.192	8.61E-10
Smoking	22506_113	Tobacco smoking: Ex-smoker	-0.2849	6.91E-10
Smoking	22506_114	Tobacco smoking: Never smoked	0.3183	1.31E-13
Smoking	6157_3	Why stopped smoking: Health precaution	0.4017	3.75E-14
Smoking	1249	Past tobacco smoking	0.2408	5.95E-17
Smoking	2644	Light smokers, at least 100 smokes in lifetime	-0.4093	2.88E-19
Smoking	1259	Smoking/smokers in household	-0.6219	4.11E-21
Smoking	1269	Exposure to tobacco smoke at home	-0.589	3.55E-24
Smoking	1279	Exposure to tobacco smoke outside home	-0.4604	1.02E-28
Smoking	2867	Age started smoking in former smokers	0.5045	3.72E-29
Smoking	20116_0	Smoking status: Never	0.368	7.27E-41
Smoking	1787	Maternal smoking around birth	-0.5114	8.23E-52
Smoking	20116_2	Smoking status: Current	-0.5304	2.68E-65
Smoking	1239	Current tobacco smoking	-0.5415	8.12E-73
Time	6160_1	Leisure/social activities: Sports club or gym	0.3297	2.68E-19

Time	6160_4	Leisure/social activities: Adult education class	0.4723	1.80E-25
Time	6160_5	Leisure/social activities: Other group activity	0.6606	1.81E-65
Time	6160_100	Leisure/social activities: None of the above	-0.6188	1.14E-83
Time	1070	Time spent watching television (TV)	-0.5255	3.55E-88
Time	1050	Time spend outdoors in summer	-0.5484	3.79E-110
Time	1060	Time spent outdoors in winter	-0.4416	7.21E-37
Time	1120	Weekly usage of mobile phone in last 3 months	-0.2907	6.23E-18
Time	1080	Time spent using computer	0.3244	1.92E-34
Time	6160_2	Leisure/social activities: Pub or social club	-0.3182	3.90E-14
Time	4290	Duration screen displayed	-0.3573	7.53E-27
Transportation	6162_3	Types of transport used (excluding work): Public transport	0.2087	3.72E-06
Transportation	6143_1	Transport type for commuting to job workplace: Car/motor vehicle	-0.2891	3.19E-08
Transportation	6162_1	Types of transport used (excluding work): Car/motor vehicle	0.1658	3.40E-05
Transportation	6162_2	Types of transport used (excluding work): Walk	0.3996	7.69E-24
Transportation	6162_4	Types of transport used (excluding work): Cycle	0.3274	1.04E-14
Trauma	20488	Physically abused by family as a child	-0.2647	6.14E-09
Trauma	20523	Physical violence by partner or ex-partner as an adult	-0.3981	4.45E-11
Workplace	22607_0	Workplace very cold: Rarely/never	0.4186	2.82E-11
Workplace	22610_1	Workplace full of chemical or other fumes: Sometimes	-0.5072	2.52E-11
Workplace	22608_2	Workplace very hot: Often	-0.5035	1.63E-13
Workplace	777	Frequency of travelling from home to job workplace	-0.4964	1.39E-15
Workplace	6143_3	Transport type for commuting to job workplace: Public transport	0.4021	4.12E-16
Workplace	22609_2	Workplace very dusty: Often	-0.5149	1.42E-17
Workplace	6143_4	Transport type for commuting to job workplace: Cycle	0.4416	8.59E-18
Workplace	22607_1	Workplace very cold: Sometimes	-0.5057	9.66E-20
Workplace	22606_2	Workplace very noisy: Often	-0.6013	4.74E-27
Workplace	4825	Noisy workplace	-0.5184	8.31E-29

b. Local Genetic Correlation

To get a precise quantification of which genomic regions disproportionately contribute to the genome-wide genetic correlation, ρ-HESS (Heritability Estimation from Summary Statistics) (Shi et al., 2017) was used to quantify the correlation between pairs of traits due to genetic variation at a small region in the genome. Figure C.b.2 shows local genetic correlation and local heritability estimates across 22 autosomes of religious attendance and depression. None of the local genetic correlations was statistically significant, and the local heritability was very small, specifically below 0.05%, without statistical significance. Thus, for complex traits such as depression and religious attendance, a strong local genetic correlation was not observed, and the overall genetic correlations and heritability were from the accumulation of the tiny genetic influence across the whole genome.

Figure C.b.2 Local genetic correlation between religious attendance and depression



D. GWAS by Subtraction

There are five parts in this section - biological annotations on religious attendance from the original GWAS summary statistics (Day et al., 2018), and four GWAS of "religious-without-sports/gym," "religious-with-sports/gym," "religious-without-pub/social," and "religious-with-pub/social" from the GWAS by subtraction (Demange et al., 2021) analysis. MAGMA (Leeuw et al., 2015) gene analyses were used for producing the Manhattan plots of gene-based tests and the tissue expression analysis (GTEx v8 53 tissue types). Positional mapping and FUMA (Watanabe et al., 2017)were used for creating gene expression heatmaps (GTEx v8 54 tissue types).

a. Religious attendance

Figure D.a.1 Manhattan plot of the religious attendance GWAS (gene-based test - 45 genes)[1]

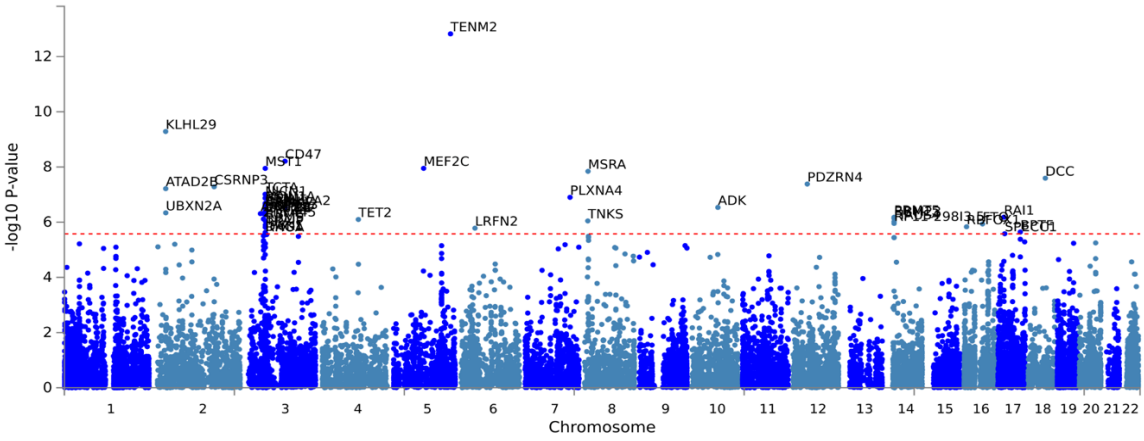
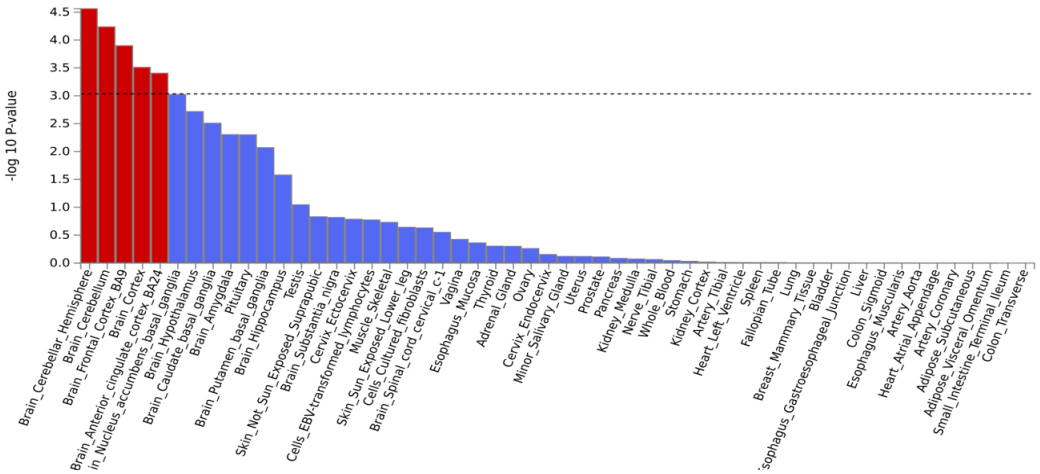


Figure D.a.2 MAGMA tissue expression analysis of religious attendance



[1] Input SNPs were mapped to 18884 protein-coding genes. Genome-wide significance (red dashed line in the plot) was defined at P = 0.05/18884 = 2.648e-6.

b. Religious-without-sports/gym

Figure D.b.1 Manhattan plot of SNP associations with "religious-without-sports/gym"

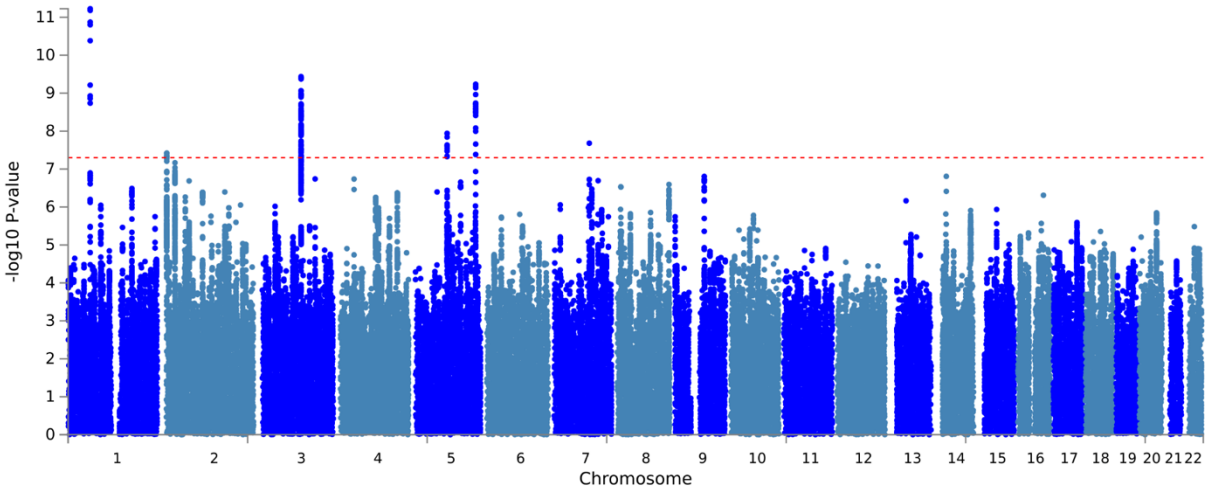
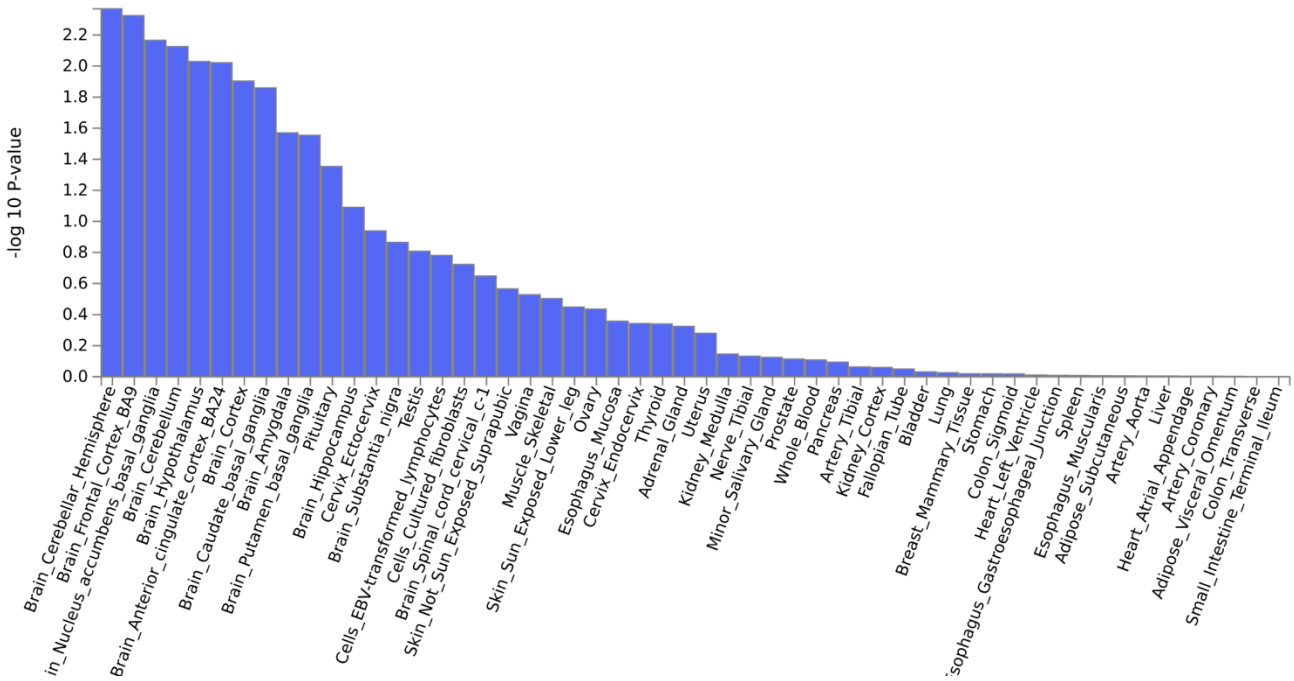


Figure D.b.2 MAGMA tissue expression analysis of "religious-without-sports/gym"



c. Religious-with-sports/gym

Figure D.c.1 Manhattan plot of SNP associations with "religious-with-sports/gym"

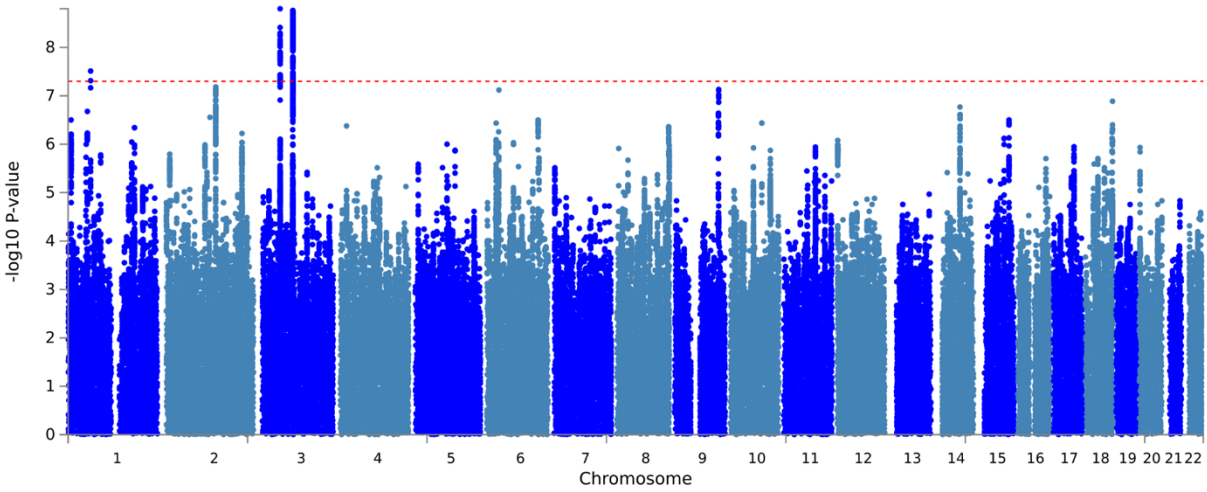
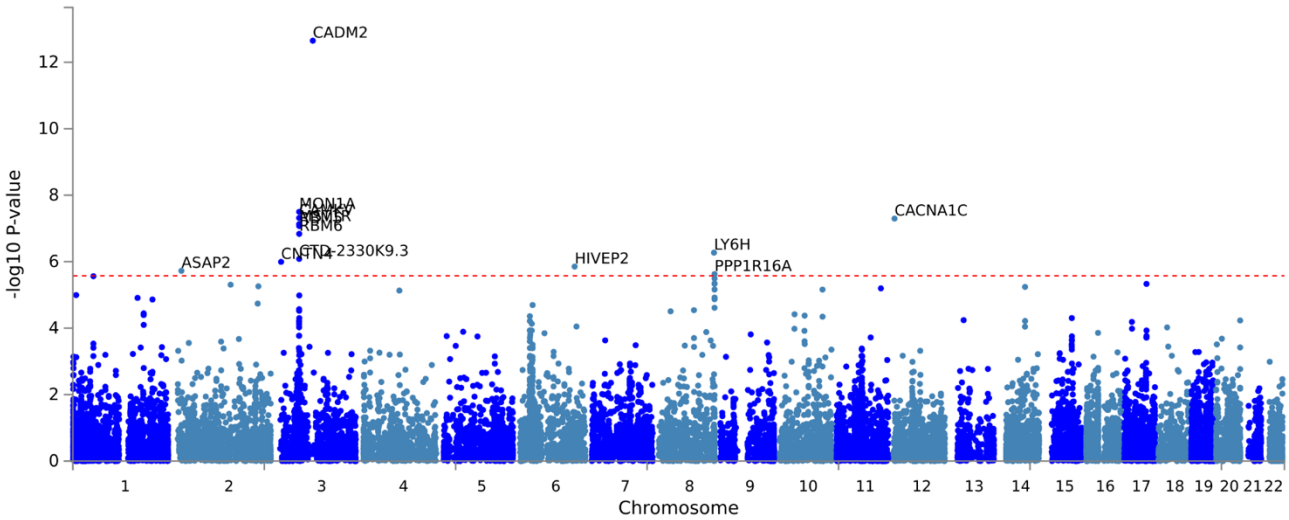


Figure D.c.2 Manhattan plot of "religious-with-sports/gym" GWAS (gene-based test - 12 genes)[2]



[2] Input SNPs were mapped to 18820 protein coding genes. Genome wide significance (red dashed line in the plot) was defined at P = 0.05/18820 = 2.657e-6.

Figure D.c.3 MAGMA tissue expression analysis of "religious-with-sports/gym"

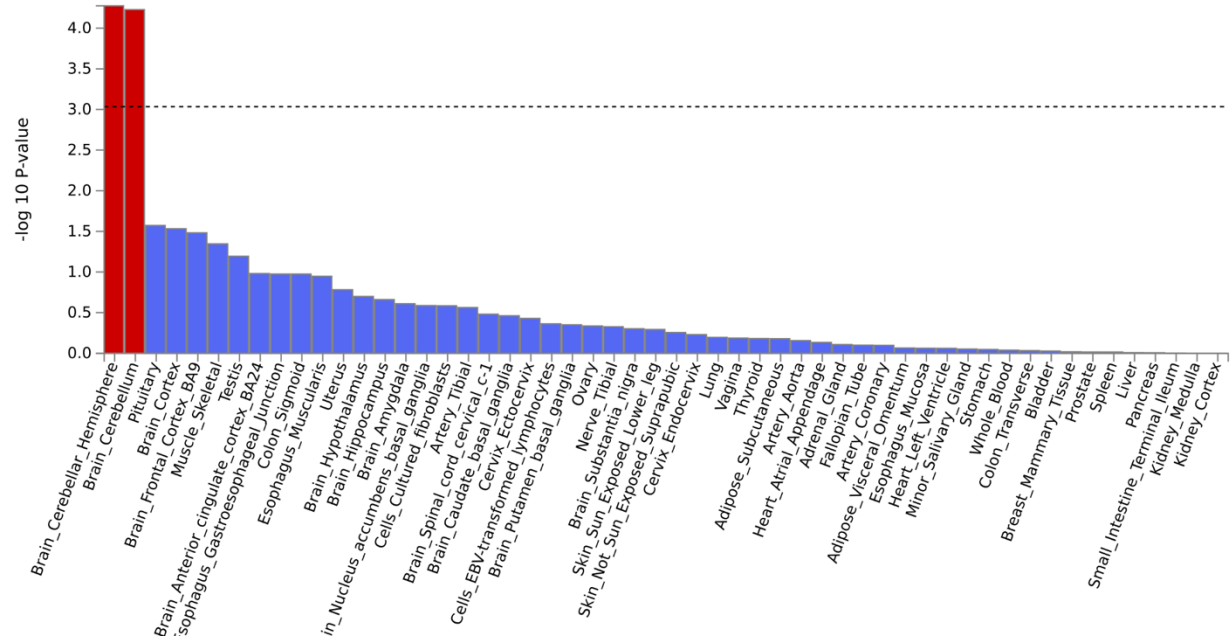
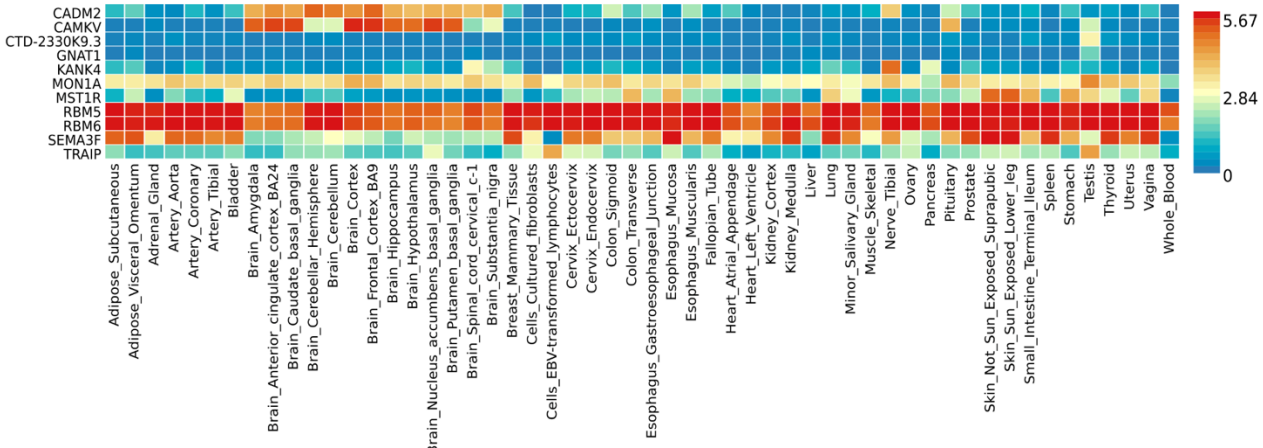


Figure D.c.4 Gene expression heatmap of "religious-with-sports/gym" (11 genes)



d. Religious-without-pub/social

Figure D.d.1 Manhattan plot of SNP associations with "religious-without-pub/social"

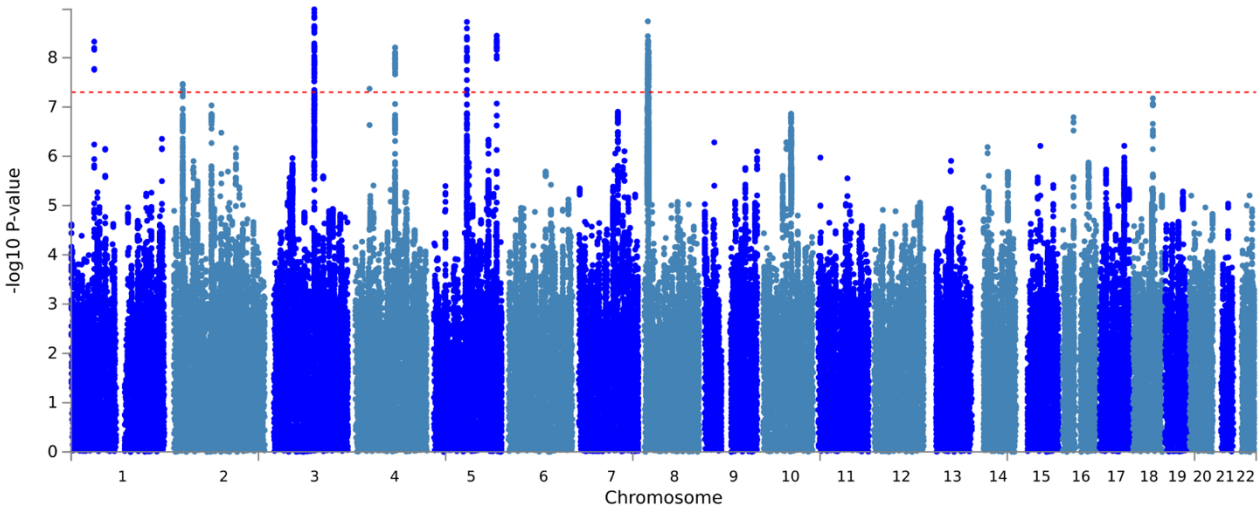
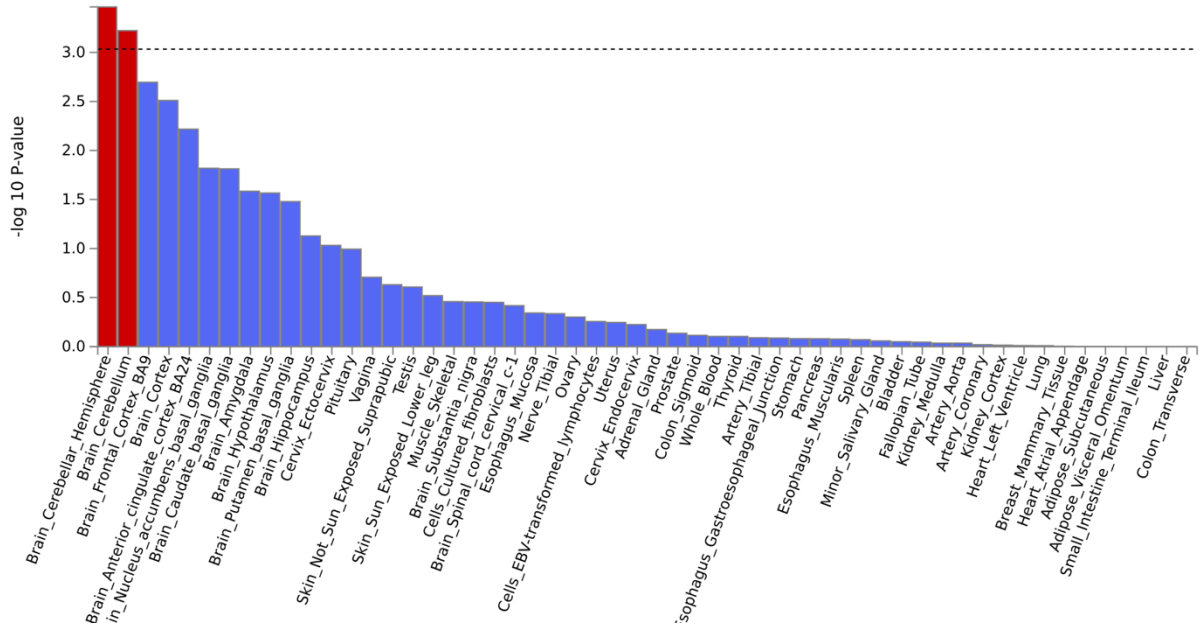


Figure D.d.2 MAGMA tissue expression analysis of "religious-without-pub/social"



e. Religious-with-pub/social

Figure D.e.1 Manhattan plot of SNP associations with "religious-with-pub/social"

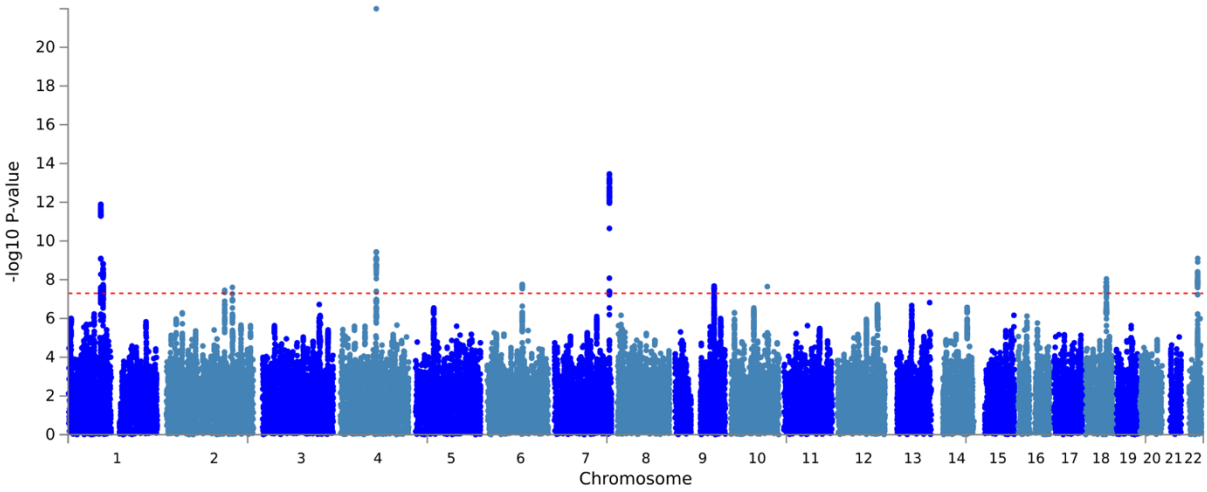
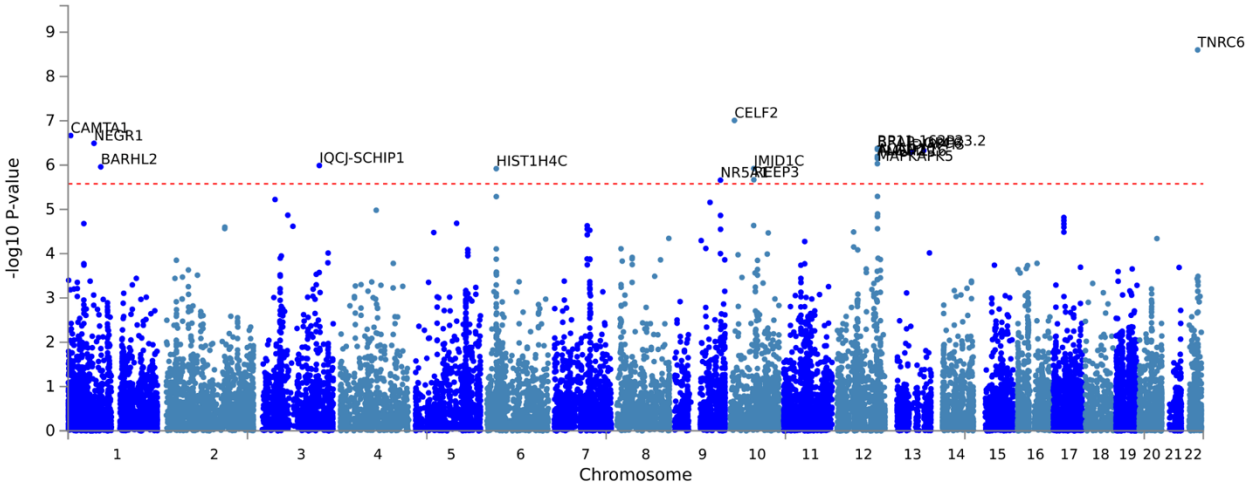


Figure D.e.2 Manhattan plot of "religious-with-pub/social" GWAS (gene-based test - 11 genes)[3]



[3] Input SNPs were mapped to 18820 protein coding genes. Genome wide significance (red dashed line in the plot) was defined at P = 0.05/18820 = 2.657e-6.

Figure D.e.3 MAGMA tissue expression analysis of "religious-with-pub/social"

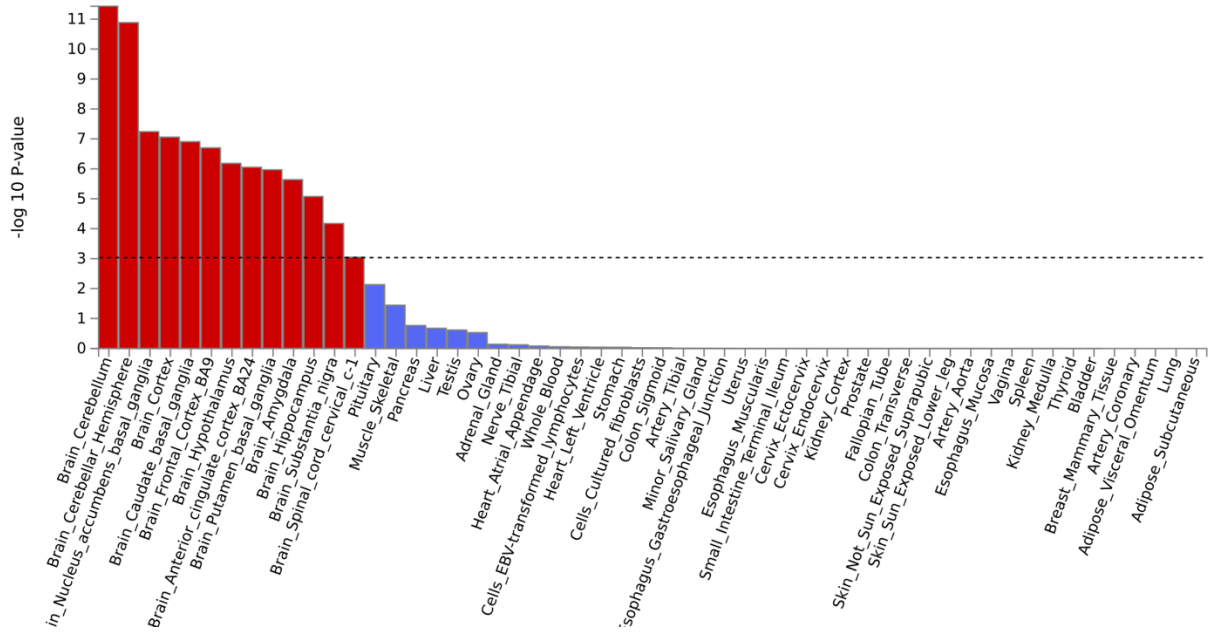
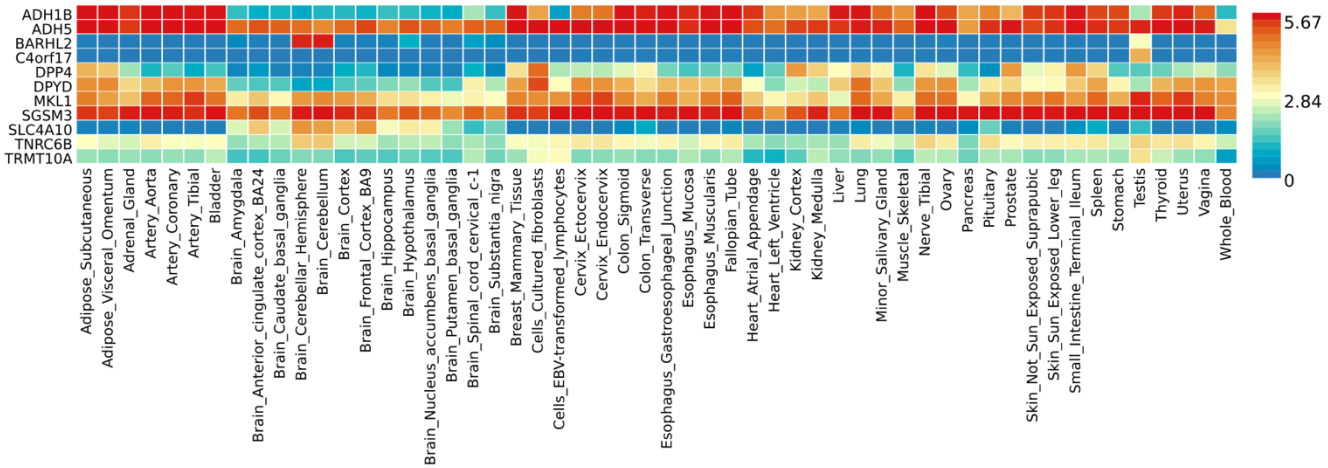


Figure D.e.4 Gene expression heatmap of "religious-with-pub/social" (11 genes)



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Chapter 2 Religious assortative mating and differential fertility among US older adults

1.Introduction

Religious assortative mating has been widely observed in the human population (Fieder & Huber, 2016). Prior studies of religious assortative mating have noticed a rise of religious intermarriage in the US since the 1950s with the general trend of secularization, more accepting attitudes towards religious intermarriage, and increasing importance of educational homogamy (Kalmijn, 1991; Putnam et al., 2012; Rosenfeld, 2008; Schwadel, 2010). Recent studies also suggest that religion remains a relevant and important factor for assortative mating and reproductive behaviors, even for younger adults in the US, especially among non-Hispanic whites (Fieder & Huber, 2016; McClendon, 2016). Not only has religious homogamy been found to be associated with a higher number of children, but also, more religious individuals have more children, on average, than less religious ones (Fieder & Huber, 2016). By comparing religion, religiosity, and fertility in the US and Europe, Frejka and Westoff (2008) have found that American women are more religious than European women, and the more devout have more children, which may partly explain higher US fertility compared to Europe as religion is important in the life of one-half of American women. Religion also plays a role in marital stability and marital satisfaction. Interfaith

unions generally have higher dissolution rates than intrafaith ones (Boulis,2022; Heaton, 1984; Lehrer & Chiswick, 1993).

Incorporating genetic data to investigate religious homogamy can help us better understand how religious attendance could persist over time and how religion could influence human evolution through assortative mating and differential fertility (Richerson et al., 2010). For religion, religious practices, and religious intensity to transmit intergenerationally, religious parents play an important role in raising their children religiously by "making costly decisions to influence their children's religious behaviors" (Bar-El et al., 2013; Bisin et al., 2004) and passing on genetic endowment for religious attendance to their biological children (Bulbulia, 2004; Fieder & Huber, 2016). For example, religious parents may need to spend time and effort teaching their children about religious values, taking them to religious services, and providing them with religious education. These efforts are considered costly because they require time and resources that could be spent on other activities. However, such investments are crucial for religious parents to ensure the continuity of religious practices and beliefs within their family and community.

Previous twin studies produced widely different estimates of the heritability of religiosity ranging from 0 to 0.56. The shared environmental factors in childhood and adolescence

seemed to contribute more to the familial resemblance of religiosity (Koenig & McGue, 2011). According to a twin study (Kendler & Myers, 2009), religiosity measured by church attendance has a higher heritability among adults (0.53) compared to young children (around 0.25). Furthermore, their research revealed that the genetic correlation between religious attendance and substance use is higher among adults than adolescents. Their results suggest that the relationship between religious attendance and other demographic behaviors may change over human development. In adulthood, the impact of one's genetic predisposition towards religious attendance may be more pronounced, as the church attendance of younger children is likely to be influenced by a broader range of family and social-environmental factors.

Based on the GWAS study (Day et al., 2018) of religious attendance mentioned in Chapter 1, the SNP-based heritability is 4.6%. If individuals who are more religious have greater rates of reproduction compared to those who are less religious, then the frequency of alleles linked to religious attendance may increase within a population, despite the heritability being less than 5%. The size of the fertility differentials would impact the pace of genetic evolution and the share of the religious population in the future (Fieder & Huber, 2016; Hedrick, 2016; Richerson et al., 2010; Rowthorn, 2011). This chapter aims to answer the following research

questions by incorporating genetic data from the Health and Retirement Study (HRS) and the Wisconsin Longitudinal Study (WLS).

Research questions:

1. **What is the trend of religious assortative mating across generations among older non-Hispanic white adults in the United States? Have correlations between partners' polygenic index (PGI) of religious attendance changed over birth cohorts? Can the inclusion of the religious attendance PGI improve the prediction of spousal religious attendance?**
2. **Has the genetic covariance between fertility and religious attendance changed over time? Can incorporating the religious attendance PGI improve the prediction accuracy of fertility and account for the variability in fertility levels among individuals?**
3. **What are the direct and indirect genetic effects of religious attendance on fertility?**

2.Literature Review

Recent studies using genetic data to examine assortative mating in humans have focused on nonreligious traits, such as height, Body Mass Index (BMI), and education (Barban, De Cao, et al., 2016; Conley et al., 2016; Domingue et al., 2014; Guo et al., 2014; Robinson et al.,

2017; Zou et al., 2015). Genetic evidence of assortative mating is found by calculating the genetic similarity (genome-wide sharing of SNPs) between married couples and testing whether the spousal similarity is significantly larger than the expected similarity from two non-related individuals in the population (Domingue et al., 2014; Guo et al., 2014; Robinson et al., 2017; Zou et al., 2015). According to Domingue et al. (2014), "the genetic similarity among spouses only explains at most 10% of the assortative mating by education levels" in a nationally representative sample of non-Hispanic white US adults from HRS. Using a sample of Latino couples from the Genes-Environments & Admixture in Latino Americans II (GALAII) study, the genomic ancestry assortment is found to be comparable or stronger than the education assortment (Zou et al., 2015). Using samples (24,662 spousal pairs in total) from various data sources, there is a correlation among partners at trait-associated loci for height, BMI, waist-to-hip ratio, blood pressure, and educational attainment (Robinson et al., 2017). Whether there is a correlation between spouses at trait-associated genetic loci for religious attendance remains unknown.

The study analyzing birth cohorts from 1920 to 1955 using data from the HRS found that there is a lack of genetic correlation between educational assortative mating and fertility (Conley et al., 2016). Although there is an increase in assortative mating based on education at the phenotypic level, there is no corresponding increase at the genotypic level.

Additionally, the study did not identify any evidence suggesting that genes play a role in the fertility differential across different education levels. Currently, it is uncertain whether the change in religious assortative mating at the phenotypic level is accompanied by similar changes at the genotypic level. Furthermore, it remains unclear whether the observed fertility differences across various levels of religious attendance are influenced by genetic factors.

Parents can influence the religious attendance of their children through the transmission of certain alleles and the impact of inherited family environments through non-transmitted alleles. Earlier research has identified the presence of genetic nurture effects on children, which refer to the indirect genetic impact of non-transmitted alleles on parents and other relatives (Koellinger & Harden, 2018; Kong et al., 2018; Wang et al., 2021). Specifically, Kong *et al.* (2018) demonstrate that non-inherited components of parental genotype can predict the educational achievement of their children using genotyped trios [parents and their offspring(s)]. Based on a meta-analysis (Wang et al., 2021) of 12 studies that investigated the genetic nurture effects in older non-Hispanic white adults in the United States, "naive estimates" of the genetic nurtureeffect were obtained. The analysis suggested that the genetic nurture effects were notable and consistent across diverse cohorts, countries, and educational assessments. However, it is important to note that the estimates may be biased due to the lack of control for grandparental genetic effects, which are necessary to obtain true genetic nurture

effects. Additionally, while the genetic nurture estimate may be upwardly biased by population stratification, it may also be downwardly biased by the assumption that the true weights for indirect effects are the same as for the direct effec (Visscher et al., 2008). The analysis based on a regular GWAS, rather than a within-family GWAS may be more prone to biases due to population stratification, which can arise when different subpopulations within a larger population have different frequencies of genetic variants. Therefore, caution must be exercised in interpreting the results.

The religious attendance polygenic index (PGI) obtained from regular genome-wide association studies (GWAS) comprises both direct genetic effects and genetic nurture effects, biased by population stratification; Thus, the PGI coefficients obtained through between-family regressions are susceptible to bias due to genetic nurture (Kong et al., 2018; Trejo & Domingue, 2018; Young et al., 2022). To date, most research on genetic nurture effects focused on education; no research has been conducted to estimate the direct genetic effects of religious attendance on fertility and disentangle the effects of genetic nature from those of genetic nurture on religious attendance and fertility.

While a within-family trio-based design can ideally provide an unbiased estimate of direct genetic effects, it is rare to have genotyped parental data (Kong et al., 2018; Young et al.,

2019, 2022). Young et al. (2022) have devised a novel Mendelian imputation approach that utilizes sibling data to impute missing parental genotypes and estimate direct genetic effects. Full biological siblings share on average 50% of their genetic material due to the random assortment of alleles during meiosis, which is akin to a genetic lottery (Fletcher & Lehrer, 2011; Harden, 2021; Visscher et al., 2008). Sibling design could leverage the within-family, between-sibling differences in exposure to many unobserved confounding variables such as family environments, parental genomes, and parental characteristics/behaviors (Boardman et al., 2013; Conley et al., 2007; Petersen & Lange, 2020). Further, sibling design with imputed parental genotypes can enable a more thorough examination of the contribution of genetics to complex traits, such as religious attendance and fertility, by estimating indirect genetic nurture effects from parents and siblings (Young et al., 2022).

3.Data & Methods

1. Health and Retirement Study (HRS)

To answer the assortative mating question, we restricted samples to non-Hispanic white couples who participated in the US Health and Retirement Study (HRS)[4] with genotyping data (The University of Michigan, 2020). The US Health and Retirement Study (HRS) is a nationally representative longitudinal study of individuals aged 50 and over and their

[4] The HRS (Health and Retirement Study) is sponsored by the National Institute on Aging (NIA U01AG009740) and is conducted by the University of Michigan.

spouses, who are interviewed biennially about their health, income, employment, and family characteristics. Our analysis used genotypic and phenotypic information from wave 1 (1992) to wave 14 (2018). More detailed information about the HRS sample can be found in Chapter 1. The first-marriage sample consists of a total of 2,359 pairs with at least one spouse in their first marriage, while the all-marriage sample has a total of 3,187 pairs of all available married couples from the first wave in 1992 to the fourteenth wave in 2018. Table 3.1.1 presents descriptive statistics for the spousal pairs used to answer the mating-related questions. The sample used for analyzing fertility differentials was not limited to married couples only, but included all non-Hispanic whites with available phenotypic responses and genotypic data (N=10,472). Table 3.1.2 presents descriptive statistics for the entire sample that was utilized to examine fertility differentials, while Supplementary Materials Table B.1 contains descriptive statistics for females and males separately.

Table 3.1.1 HRS descriptive statistics, non-Hispanic white spouses with both genotypic data and valid phenotypic responses

	First marriages sample (2,359 spousal pairs)			**All marriages sample (3,187 spousal pairs)**		
Variables	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
Female birthyear	1941.91	10.55	[1911, 1979]	1942.46	10.55	[1911, 1979]
Male birthyear	1939.16	10.38	[1910, 1975]	1939.29	10.38	[1910, 1975]
Female REL PGI	0.01	1.00	[-3.43, 3.34]	0.01	0.99	[-3.89, 3.34]

Male REL PGI	0.05	1.00	[-4.45, 3.98]	0.02	1.01	[-4.45, 3.98]
Female religious attendance [times/year]	35.98	29.82	[0, 91]	34.72	29.67	[0, 91]
Male religious attendance [times/year]	31.26	29.39	[0, 90]	30.15	29.24	[0, 90]
Female religious attendance [>=weekly]	0.44	binary	[0, 1]	0.42	binary	[0, 1]
Male religious attendance [>=weekly]	0.37	binary	[0, 1]	0.36	binary	[0, 1]

We utilized the PRSice-2 software to construct the religious attendance PGI for HRS data, and the details of this process are provided in Chapter 1. The PGI that yielded the most accurate prediction was chosen for this chapter. The PGIs were all standardized with a mean of 0 and an SD of 1 for analysis. The Number of Everborn Children (NEB) PGI was derived from a 2016 GWAS on fertility, which produced three separate GWAS summary statistics: NEBF PGI and NEBM PGI for females and males, respectively, as well as NEBC PGI for both genders combined (Barban, Jansen, et al., 2016). We used NEBC PGI to model the entire sample, comprising both females and males and employed NEBF and NEBM PGI for modeling specific genders, respectively.

To account for any potential population structure in the dataset, both the phenotypes and genotypes were residualized for the first 10 principal components derived from the genome-wide SNP data unless otherwise stated. The binary phenotype measures whether the respondent attended religious activities weekly or more, and the continuous phenotype is estimated by the annual number of religious activities attended. The number of Everborn Children (NEB) is the highest count of children that an individual has reported giving birth to or fathering. To make the coefficient of the birthyear variable more comparable to those of other standardized variables, birthyear was rescaled to one-tenth of the difference between birthyear and 1900 in the regression analysis.

Table 3.1.2 HRS descriptive statistics, non-Hispanic white participants with both genotypic data and valid phenotypic responses

	Total sample N = 10,472		
Variables	**Mean**	**SD**	**Range**
Birthyear	1939.44	11.42	[1905, 1979]
Gender - Male	0.43	binary	[0, 1]
REL PGI	0.00	1.00	[-4.45, 3.98]
NEBC PGI	0.00	1.00	[-4.61, 3.47]
Religious attendance [times/year]	31.35	29.06	[0, 91]

Religious attendance [>=weekly]	0.37	binary	[0, 1]
Number of Everborn Children (NEB)	2.49	1.62	[0, 11]

We analyzed seven models that had different combinations of covariates to predict spousal religious attendance to better understand religious assortative mating. The models were estimated separately by gender. The following are the specifications for predicting wives' religious attendance using a standardized continuous outcome and linear models with robust standard errors. The robust standard errors are calculated using a method called the sandwich estimator, which is a type of heteroscedasticity-consistent estimator[5] (Cribari-Neto, 2004). The gender subscripts "f" and "m" are used to denote females and males, respectively. The spousal pairs are identified using the "i" subscript.

- *Model 1*: $REL_{fi} = b_0 + b_1 Birthyear_{mi} + \varepsilon_{fi}$

- *Model 2*: $REL_{fi} = b_0 + b_1 Birthyear_{mi} + b_2 PGI_{mi} + \varepsilon_{fi}$

- *Model 3*: $REL_{fi} = b_0 + b_1 Birthyear_{mi} + b_2 PGI_{fi} + \varepsilon_{fi}$

- *Model 4*: $REL_{fi} = b_0 + b_1 Birthyear_{mi} + b_2 PGI_{mi} + b_3 PGI_{fi} + \varepsilon_{fi}$

- *Model 5*: $REL_{fi} = b_0 + b_1 Birthyear_{mi} + b_2 PGI_{mi} + b_3 PGI_{fi} + b_4 PGI_{mi} \times Birthyear_{mi} + \varepsilon_{fi}$

[5] The sandwich estimator "sandwiches" the variance-covariance matrix of the regression coefficients between two matrices: one matrix is the estimated variance-covariance matrix assuming equal variance across all observations, while the other matrix captures the heteroscedasticity of the residuals. The sandwich estimator is then calculated as the product of these two matrices, which produces a variance-covariance matrix that is robust to heteroscedasticity and other forms of model misspecification. We used the lm_robust function in R to compute the sandwich estimator using the residuals and covariate matrix of the linear regression model and returns the robust standard errors and t-statistics of the regression coefficients based on this estimator.

- *Model 6*: $REL_{fi} = b_0 + b_1 Birthyear_{mi} + b_2 REL_{mi} + b_3 REL_{mi} \times Birthyear_{mi} + \varepsilon_{fi}$

- *Model 7*: $REL_{fi} = b_0 + b_1 Birthyear_{mi} + b_2 PGI_{mi} + b_3 PGI_{fi} + b_4 REL_{mi} + b_5 REL_{mi} \times Birthyear_{mi} + \varepsilon_{fi}$

To predict husbands' religious attendance, the gender subscripts are simply reversed. We also used logistic regressions to predict binary religious attendance outcomes with the same combinations of predictors and top 10 principal components. Model 1, which includes only birthyear as a predictor, serves as the baseline model. Models 2 to 5 investigate the effects of incorporating different PGI variables, while Model 5 includes an interaction term to explore whether the relationship between spousal PGI and religious attendance varies depending on the birth cohort. Model 6 excludes PGIs, thereby assessing the predictability of spousal religious attendance without genotypic information. Model 7 adds both spousal PGI and self PGI to Model 6 to determine whether PGIs can enhance predictability. Given the correlation between the religious attendance PGI and religious attendance, we anticipate that the inclusion of phenotypes in Model 7 would result in spousal religious attendance capturing some of the variance that was previously attributed to PGIs in Model 4.

We estimated seven equations of the following forms to investigate changes and differentials in fertility:

- *Model 1:* $NEB_j = b_0 + b_1 Birthyear_j + b_2 Gender_j + \varepsilon_j$

- *Model 2:* $NEB_j = b_0 + b_1 Birthyear_j + b_2 Gender_j + b_3 REL__PGI_j + \varepsilon_j$

- *Model 3:* $NEB_j = b_0 + b_1 Birthyear_j + b_2 Gender_j + b_3 NEB__PGI_j + \varepsilon_j$

- *Model 4:* $NEB_j = b_0 + b_1 Birthyear_j + b_2 Gender_j + b_3 REL__PGI_j + b_4 NEB__PGI_j + \varepsilon_j$

- <u>Model 5:</u> $NEB_j = b_0 + b_1 Birthyear_j + b_2 Gender_j + b_3 REL__PGI_j + b_4 NEB__PGI_j + b_5 REL_j + \varepsilon_j$

- <u>Model 6:</u> $NEB_j = b_0 + b_1 Birthyear_j + b_2 Gender_j + b_3 REL__PGI_j + b_4 NEB__PGI_j +$

$b_5 REL_j + b_6 REL_j \times Birthyear_j + \varepsilon_j$

- <u>Model 7:</u> $NEB_j = b_0 + b_1 Birthyear_j + b_2 Gender_j + b_3 REL__PGI_j + b_4 NEB__PGI_j +$

$b_5 REL_j + b_6 REL_j \times Gender_j + \varepsilon_j$

where j indexes individuals and NEB_j is the number of everborn children reported by individual j. Model 1 serves as the baseline model with birthyear and gender as predictors, while Models 2 to 4 incorporate REL PGI, NEB PGI, or both. Model 5 adds religious attendance to Model 4, and Models 6 and 7 evaluate the inclusion of two interaction terms to investigate whether the relationship between religious attendance and fertility varies by birth cohort or gender.

2. Wisconsin Longitudinal Study (WLS)

We utilized the Wisconsin Longitudinal Study (WLS) to investigate the direct genetic effects of religious attendance on fertility, using a sample of more than 2,000 full sibling pairs with genotyping data. The WLS is a longitudinal study that began with Wisconsin high school graduates in 1957, with a randomly selected sibling added to the sample from the third wave in 1977 (Herd et al., 2014). Our analysis used genotypic and phenotypic information from wave 3 (1975 & 1977) to wave 6 (2011). The majority of WLS respondents are non-Hispanic whites, and their family background is more homogeneous in terms of socioeconomic status

than that of the HRS respondents. To avoid any bias due to population structure, we restricted our analysis to non-Hispanic whites.

We utilized the snipar (single nucleotide imputation of parents), a Python package that offers various useful features for family-based genetic analysis, to estimate direct genetic effects (Young et al., 2022). With the help of snipar, we inferred identity-by-descent (IBD) segments that are shared between siblings, imputed missing parental genotypes, and conducted polygenic index analyses using observed and imputed parental genotypes. We imputed missing parental genotypes based on sibling data from 2,122 families for 693,051 SNPs using snipar. We calculated PGIs for these families, including an average parental PGI for each family and specific PGIs for siblings. We used GWAS summary statistics from the Social Science Genetic Association Consortium to construct PGIs. Specifically, we utilized data from the GWAS studies on religious attendance (Day et al., 2018), education (Okbay et al., 2022), as well as age at first birth and the number of everborn children (Barban, Jansen, et al., 2016). All the PGIs were standardized with a mean of 0 and an SD of 1 for analysis. Descriptive statistics for all siblings with genotypic data are shown in Table 3.2.1. We excluded half-siblings and siblings without valid phenotypic responses when estimating direct genetic effects for specific phenotypes.

In Chapter 1, we utilized GWAS summary statistics and Genomic Structural Equation Modelling (SEM) to investigate whether the genetic effect of religious attendance on fertility was mediated by education. The Genomic SEM revealed the intricate genetic covariance structure, highlighting the indirect genetic pathways through education, age at first birth, and the number of sexual partners. We expanded our analysis to include education and age at first birth to explore the direct genetic effects of religious attendance on fertility using within-family data. Unfortunately, data on the number of sexual partners were not available for the WLS dataset. For each of the four traits - religious attendance (REL), education (EDU), age at first birth (AFB), and number of everborn children (NEB) - we estimated the two following models using the four different PGIs as predictors, respectively. The subscripts "i" and "j" are used to denote the family i and the sibling j. In addition, we denoted the average parental PGI from Mendelian imputation as g_i for family i.

- Model 1: $y_{ij} = \beta_0 + \beta^{dir} g_{ij} + \beta^{par} g_i + \varepsilon_{ij}$,
- Model 2: $y_{ij} = \beta_0 + \beta^{dir} g_{ij} + \beta^{sib} g_{i,-j} + \beta^{par} g_i + \varepsilon_{ij}$,

In the two models, the intercept is represented by β_0. The direct genetic effects from the proband's[6] own PGI are estimated by β^{dir}, while β^{par} represents the indirect genetic effects of non-transmitted alleles from parents using imputed parental PGI. Model 1 assumes no indirect sibling effects, while Model 2 takes into account the estimation of indirect sibling

[6] The proband here is the index case in a genetic study, and the proband's family members are subsequently evaluated to investigate direct genetic effects and patterns of inheritance.

effects measured by β^{sib}, and $g_{i,-j}$ denotes the average sibling PGI from all available siblings in family i. For most families, we only have data for two full siblings, in which case $g_{i,-j}$ would be the PGI of the other sibling. The findings for Model 1 can be seen in Figure 4.3.2, and the outcomes for Model 2 are presented in Supplementary Figure C.3. We use the term 'nontransmitted coefficient' (NTC) to refer to β^{par} , which characterizes the naïve estimate of genetic nurture effects of parental genotype. This is because NTC represents the coefficient expected for the alleles that were not transmitted to the proband after controlling for the proband's genotype in the regression, as per Young et al. (2022). In addition, population stratification and the assumption of equal weights for indirect and direct effects may bias the estimate of genetic nurture effects, making it a 'naive estimate'. To achieve a more precise estimate, it is necessary to account for grandparental genetic effects in a three-generation model. For constructing PGIs, using within-family GWAS is preferred.

Table 3.2.1 WLS descriptive statistics, non-Hispanic white siblings with genotypic data

Variables (N = 4.254 siblings with genotyping data)	**Mean**	**SD**	**Range**	**NA [number of siblings with missing values]**
Birthyear	1939.74	4.90	[1918, 1961]	0
Gender - Female	0.53	binary	[0, 1]	0
Age at First Birth (AFB)	24.88	4.56	[13, 54]	368
Number of Everborn Children (NEB)	2.63	1.64	[0, 12]	11
Years of Education (EDU)	14.49	2.63	[6, 23]	34

Religious attendance [times/year]	38.44	35.98	[0, 365]	37
Religious attendance [>=weekly]	0.46	binary	[0, 1]	37
AFB PGI	0.00	1.00	[-3.93, 3.54]	0
NEB PGI	0.00	1.00	[-4.48, 3.67]	0
EDU PGI	0.00	1.00	[-3.51, 4.18]	0
REL PGI	0.00	1.00	[-3.49, 3.56]	0

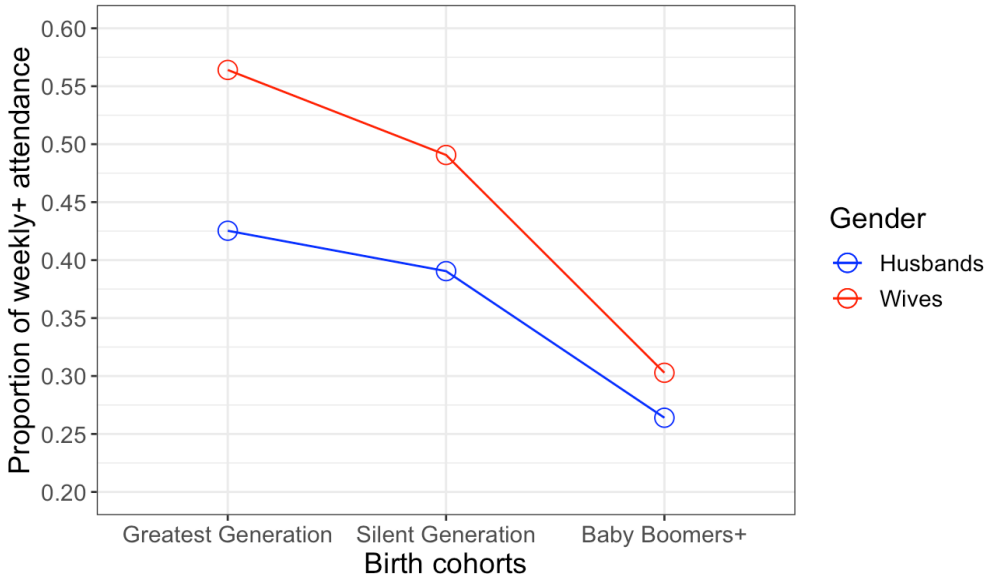
4.Results

1. Religious assortative mating

The data presented in Figure 4.1.1 indicate that religious attendance declined across generations, with a noteworthy observation that the gender gap between husbands and wives in religious attendance narrowed over cohorts. This narrowing trend was particularly prominent for Baby Boomers (individuals born between 1946 and 1964) and those born after 1964, where the gender gap was found to be the smallest. We found that women attended religious activities more frequently than men among the spousal pairs. Among the respondents from the Greatest Generation [who were born before 1926], over 50% of wives attended religious activities at least once a week. In contrast, the proportion of weekly attendance dropped to less than one-third among Baby Boomers. Furthermore, Figure A.1 in the Supplementary Materials yielded similar findings across all marriages with overall lower

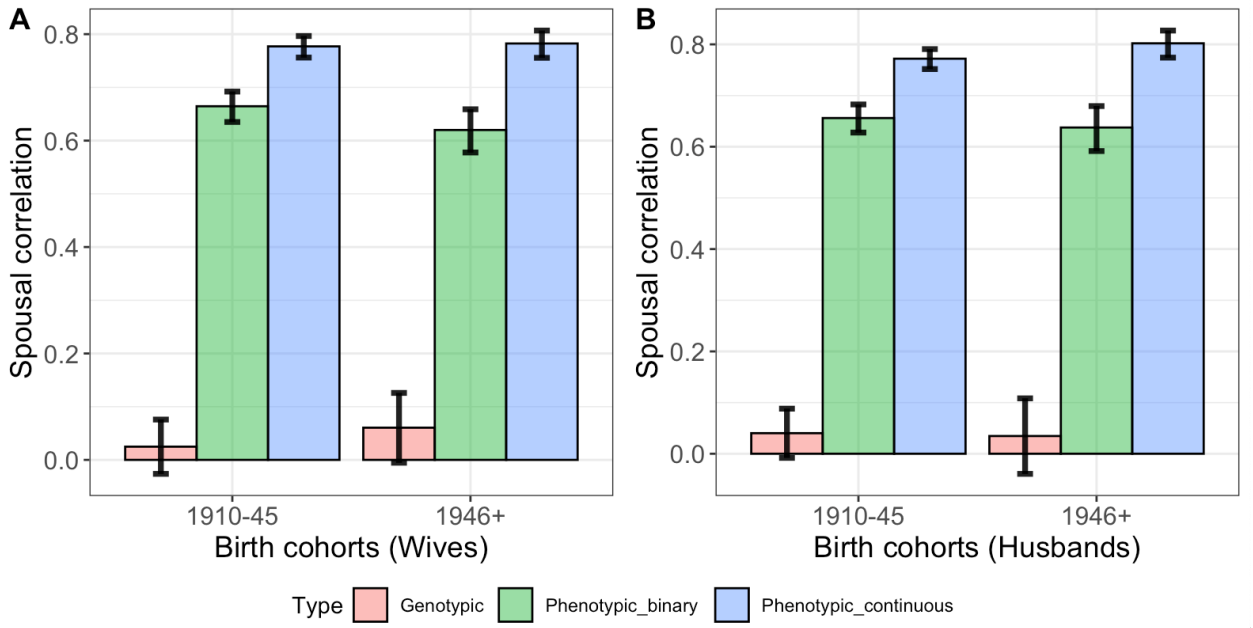
proportions, suggesting respondents who had more than one marriage tended to attend religious activities less frequently.

Figure 4.1.1 Proportion of weekly religious attendance across generations among spousal pairs [first marriages]



Deviated from random mating, the phenotypic assortative mating of religious attendance was clearly observed among HRS respondents shown in Figure 4.1.2. The error bars for correlation figures in this chapter indicate 95% confidence intervals. The estimates of phenotypic correlation were consistent across birth cohorts, with values around 0.6 for binary measurements (i.e., whether respondents attended religious activities at least once a week) and around 0.7 for continuous measurements (i.e., a standardized assessment of annual attendance of religious activities). In contrast, there is no definitive indication of genetic assortment related to religious attendance. None of the genotypic correlations in Figure 4.1.2 was significant among first marriages.

Figure 4.1.2 Spousal correlation for religious attendance phenotypes and PGI among spousal pairs in the HRS [first marriages]



However, Supplementary Figure A.2 shows a statistically significant genotypic correlation with a point estimate closer to 0.1 for all marriages with wives born after 1945. Figure A.4 and Figure A.5 from the Supplementary Materials depict spousal correlations within more specific birth cohorts. Both wives and husbands who were born between 1940 and 1949 had significant genotypic correlations. There was no apparent indication of genetic assortative mating observed among other birth cohorts.

Tables 4.1.3 and 4.1.4 display coefficients from seven different models aimed at predicting standardized religious attendance phenotypes, which have been residualized using the top 10 principal components. Model 1 uses only spousal birthyear as a predictor and serves as a baseline model. Spousal birthyears are significantly correlated with a correlation coefficient

of 0.90 and a 95% confidence interval of [0.891, 0.906]. Models 2 and 3 add the spousal PGI and self-PGI, respectively, to the first model. Both spousal and self-PGI are significantly associated with religious attendance. In Model 3, self-PGI has a larger coefficient than spousal PGI in Model 2 when predicting wives' religious attendance, leading to an increase of almost 1% in the variance explained compared to Model 1, which is larger than the increase seen in Model 2. However, in predicting husbands' religious attendance in Figure 4.1.4, the coefficients and R^2 values of Models 2 and 3 are more similar. Model 4 incorporates both spousal PGI and self-PGI, leading to an R^2 increase of over 1% when compared to Model 1, while spousal PGI remains significant. Model 5 shows no evidence of a significant interaction effect between spousal PGI and birthyear.

Model 6 builds upon Model 1 by including spousal religious attendance and its interaction term with birthyear, without using any genotypic information. The interaction term is s significant only for wives' religious attendance, indicating that the negative association between wives' religious attendance and birthyear weakens for husbands who attend religious services more frequently. Model 6 has an R^2 value of over 60%, which is much higher compared to Model 5 (<5%), where birthyear and PGIs are predictors. When both genotypic and phenotypic information of spousal religious attendance and self-PGI are included in Model 7, spousal PGI becomes insignificant, and the R^2 value increases by only 0.1%

compared to Model 6. However, self-PGI remains significant with a smaller coefficient in predicting religious attendance compared to Model 4.

Table A.6 and Table A.7 in the Supplementary Materials illustrate the seven models used to predict religious attendance for wives and husbands in all marriages, respectively. The interaction term in Model 7 was statistically significant only for husbands' religious attendance in all marriages, with a small negative value. This suggests that the positive correlation between wives' religious attendance and husbands' religious attendance weakens for younger wives. Tables A.8 to A.11 present the results of logistic regression models, which predict the binary outcome of religious attendance, and have similar findings to those of the linear regression models. Model 7, which includes an interaction term, does not have any significant interaction effect in these logistic models. Instead of using a residualized outcome variable of the principal components, we included the top 10 principal components as controls in the logistic models, and the sixth principal component consistently shows a negative and significant association with religious attendance. This indicates that the genetic ancestry variation captured by the sixth principal component may have a consistent negative impact on religious attendance.

Table 4.1.3 Predicting wives' religious attendance among spousal pairs in the HRS [first marriages][7]

	Wives Model1	Model2	Model3	Model4	Model5	Model6	Model7
(Intercept)	0.711***	0.707***	0.706***	0.703***	0.705***	0.229***	0.229***
	(0.078)	(0.078)	(0.077)	(0.077)	(0.077)	(0.052)	(0.052)
m_birthyear	−0.181***	−0.181***	−0.180***	−0.180***	−0.180***	−0.060***	−0.060***
	(0.019)	(0.019)	(0.019)	(0.019)	(0.019)	(0.013)	(0.012)
m_REL_PGI		0.069***		0.065**	0.013		−0.001
		(0.021)		(0.021)	(0.077)		(0.013)
f_REL_PGI			0.096***	0.093***	0.093***		0.032*
			(0.021)	(0.021)	(0.021)		(0.014)
m_birthyear × m_REL_PGI					0.013		
					(0.019)		
m_REL_stdz						0.680***	0.676***
						(0.050)	(0.050)
m_birthyear × m_REL_stdz						0.027*	0.027*
						(0.012)	(0.012)
Num.Obs.	2359	2359	2359	2359	2359	2359	2359
R2	0.034	0.038	0.043	0.047	0.047	0.620	0.621
R2 Adj.	0.033	0.038	0.042	0.045	0.045	0.620	0.620
AIC	6712.7	6703.5	6693.2	6685.1	6686.6	4515.3	4513.4
BIC	6730.0	6726.6	6716.3	6713.9	6721.2	4544.2	4553.8
RMSE	1.00	1.00	1.00	1.00	1.00	0.63	0.63

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Table 4.1.4 Predicting husbands' religious attendance among spousal pairs in the HRS [first marriages]

	Husbands Model1	Model2	Model3	Model4	Model5	Model6	Model7
(Intercept)	0.743***	0.741***	0.734***	0.732***	0.729***	0.098+	0.096+
	(0.082)	(0.082)	(0.082)	(0.082)	(0.082)	(0.053)	(0.054)
f_birthyear	−0.173***	−0.173***	−0.172***	−0.172***	−0.171***	−0.020	−0.020
	(0.019)	(0.019)	(0.019)	(0.019)	(0.019)	(0.013)	(0.013)
f_REL_PGI		0.083***		0.080***	0.197*		0.007
		(0.020)		(0.020)	(0.083)		(0.014)
m_REL_PGI			0.085***	0.082***	0.083***		0.035**
			(0.020)	(0.021)	(0.021)		(0.013)
f_REL_PGI × f_birthyear					−0.028		
					(0.019)		
f_REL_stdz						0.806***	0.805***
						(0.051)	(0.051)
f_birthyear × f_REL_stdz						−0.009	−0.009
						(0.012)	(0.012)
Num.Obs.	2359	2359	2359	2359	2359	2359	2359
R2	0.033	0.040	0.040	0.046	0.047	0.616	0.617
R2 Adj.	0.033	0.039	0.039	0.045	0.046	0.616	0.616
AIC	6653.5	6639.0	6637.9	6624.6	6624.5	4478.9	4475.3
BIC	6670.8	6662.1	6661.0	6653.4	6659.1	4507.8	4515.6
RMSE	0.99	0.99	0.99	0.98	0.98	0.62	0.62

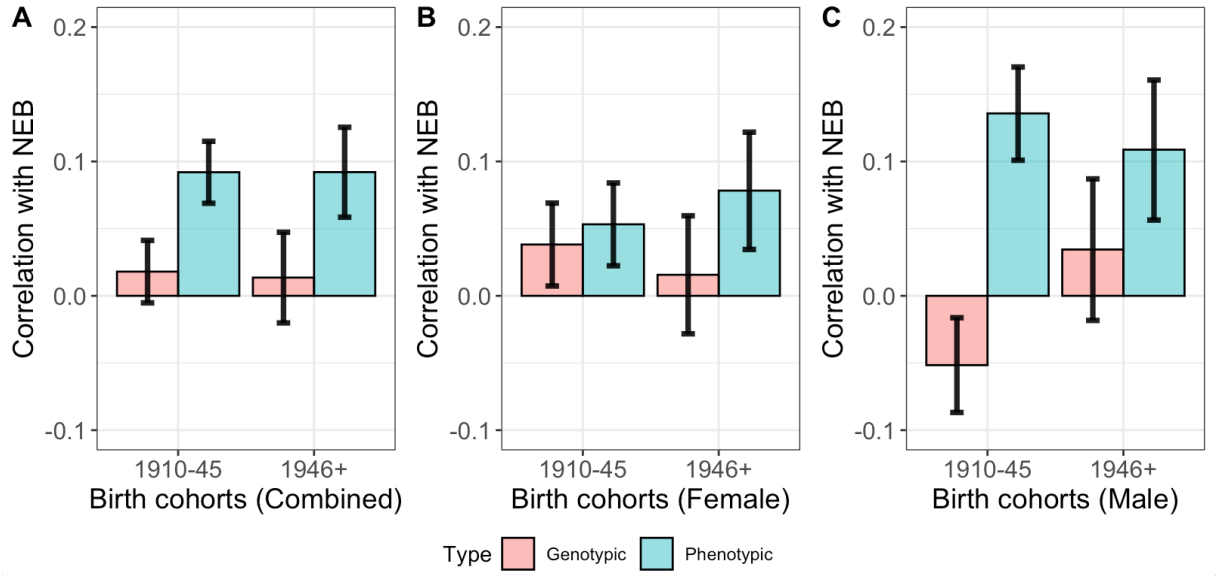
+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

[7] The prefixes "m_" and "f_" denote predictors of husbands and wives, respectively. The postfix "_stdz" indicates that the variable has been standardized. AIC is short for Akaike Information Criterion, which is a model selection criterion that balances the fit of the model to the data with the complexity of the model. Lower AIC values indicate better model fit. BIC is Bayesian Information Criterion, which is a model selection criterion similar to AIC, but with a stronger penalty for model complexity. Lower values indicate better model fit. RMSE stands for Root Mean Square Error and is a statistical measure of the difference between predicted and observed values in a regression. It is calculated by taking the square root of the average of the squared differences between the predicted and observed values. The lower the RMSE, the better the fit of the model to the data.

2. Differential Fertility

Figure 4.2.1 shows a consistent positive and statistically significant phenotypic correlation between religious attendance and the number of everborn children with error bars indicating the 95% confidence intervals. However, the correlation coefficients are relatively small, less than 0.15. In contrast, there is no significant genotypic correlation observed for both genders combined. Females born between 1910 and 1945 show a positive genotypic association, while males born between 1910 and 1945 show a negative association.

Figure 4.2.1 Genotypic and phenotypic correlations between religious attendance (REL) and number of everborn children (NEB) among non-Hispanic whites in the HRS



Further analysis in Figure B.3 of the Supplementary Materials also demonstrates gender-based differences in genotypic and phenotypic correlations among specific cohorts. Similarly, female birth cohorts of the 1940s show a positive genotypic correlation between the religious attendance PGI and the number of everborn children PGI, whereas male cohorts of the 1930s

show a negative genotypic correlation. No statistically significant genotypic correlations were found among younger cohorts.

Table 4.2.2 consists of seven models that predict the number of everborn children for non-Hispanic white Americans in the HRS dataset with valid phenotypic responses and genotypic data. Model 1 serves as the baseline model, with gender and birthyear as predictors. As prior research has demonstrated (Conley et al., 2016; Rindfuss & Sweet, 1977), the number of offspring is negatively associated with the birthyear among HRS respondents. The correlation between gender and fertility is statistically significant, indicating that male respondents have fewer children compared to females. Model 3 introduces the PGI of the number of everborn children for both genders combined (NEBC), while Models 2 and 4 add religious attendance PGI to Models 1 and 3, respectively. As the coefficients of other variables show little change and there is no increase in the R^2 value by adding religious attendance PGI, this indicates that the inclusion of religious attendance PGI does not improve the prediction of fertility in HRS. In contrast, the addition of NEBC PGI results in an approximately 8 percentage point increase in R^2, from 5.7% in Model 1 to 13.8% in Model 3. The NEBC PGI explains more variance in fertility than gender and birthyear combined.

In Model 5, the inclusion of religious attendance as an additional predictor leads to a greater amount of explained variance of fertility when compared to Model 4. Model 5 also confirms the positive phenotypic correlation between religious attendance and fertility with statistical significance ($P < 0.001$) after controlling for two PGIs. Model 6 introduces an interaction term between religious attendance and birthyear, while Model 7 includes an interaction term between religious attendance and gender. Only the interaction between religious attendance and gender is statistically significant, which implies that the positive correlation between religious attendance and fertility is notably stronger among males who attend religious services more frequently. Supplementary Table B.4 presents comparable findings obtained from Poisson regression models, where the number of everborn children is specified as a Poisson-distributed outcome variable, and the top 10 principal components are incorporated as predictors in the models. In addition, Table B.5 and B.6 in Supplementary Materials predict the number of everborn children by gender. Similar to the linear models, the inclusion of religious attendance PGI did not significantly improve model predictability, and the gender-specific fertility PGI explained more variance in fertility compared to other predictors, including birthyear, gender, and religious attendance

Table 4.2.2 Predicting the standardized number of children everborn (NEB) for non-Hispanic whites in the HRS with genotypic data

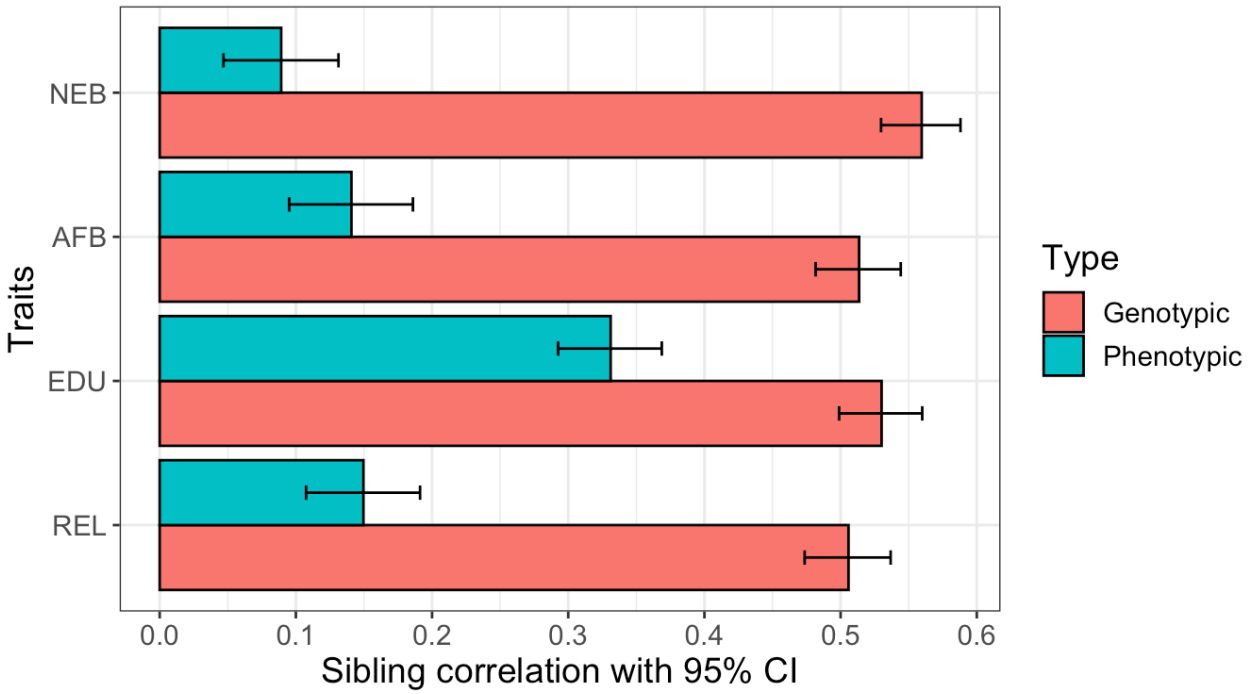
	Model1	Model2	Model3	Model4	Model5	Model6	Model7
(Intercept)	0.850***	0.851***	0.889***	0.890***	0.830***	0.830***	0.835***
	(0.038)	(0.038)	(0.037)	(0.037)	(0.037)	(0.037)	(0.037)
Birthyear	−0.208***	−0.208***	−0.219***	−0.220***	−0.206***	−0.206***	−0.207***
	(0.009)	(0.009)	(0.008)	(0.008)	(0.008)	(0.009)	(0.008)
GenderMale	−0.067***	−0.067***	−0.057**	−0.057**	−0.041*	−0.041*	−0.039*
	(0.019)	(0.019)	(0.018)	(0.018)	(0.018)	(0.018)	(0.018)
REL_PGI		−0.003		−0.008	−0.015+	−0.015+	−0.016+
		(0.010)		(0.009)	(0.009)	(0.009)	(0.009)
NEBC_PGI			0.282***	0.282***	0.282***	0.282***	0.282***
			(0.010)	(0.010)	(0.010)	(0.010)	(0.010)
REL_stdz					0.085***	0.073+	0.055***
					(0.009)	(0.038)	(0.012)
REL_stdz × Birthyear						0.003	
						(0.009)	
REL_stdz × GenderMale							0.069***
							(0.019)
Num.Obs.	10 472	10 472	10 472	10 472	10 472	10 472	10 472
R2	0.057	0.057	0.138	0.138	0.145	0.145	0.146
R2 Adj.	0.057	0.057	0.138	0.138	0.145	0.144	0.146
AIC	29 106.9	29 108.8	28 171.8	28 172.9	28 091.8	28 093.7	28 079.7
BIC	29 135.9	29 145.1	28 208.0	28 216.5	28 142.6	28 151.7	28 137.7
RMSE	0.97	0.97	0.93	0.93	0.92	0.92	0.92

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

3. Direct genetic effects of religious attendance and fertility

On average, siblings have an additive genetic correlation of 0.50 because the inheritance of alleles from parents to offspring is randomized during meiosis (Fisher, 1919; Fletcher, 2011; Selzam et al., 2019). Figure 4.3.1 demonstrates that the genotypic correlations among WLS siblings are approximately 0.5 for the traits except for the number of everborn children, which has a point estimate of 0.56 and a 95% confidence interval of [0.53, 0.59]. All four traits show significant positive phenotypic correlations between siblings. The highest phenotypic correlation of around 0.3 is observed for education, while the other three traits have phenotypic correlations of less than 0.2. The specific estimates for Figure 4.3.1 can be found in Supplementary Table C.1.

Figure 4.3.1 Sibling correlation of four traits - Number of Everborn Children (NEB), Age at First Birth (AFB), Years of Education (EDU) and Religious Attendance (REL) in the WLS

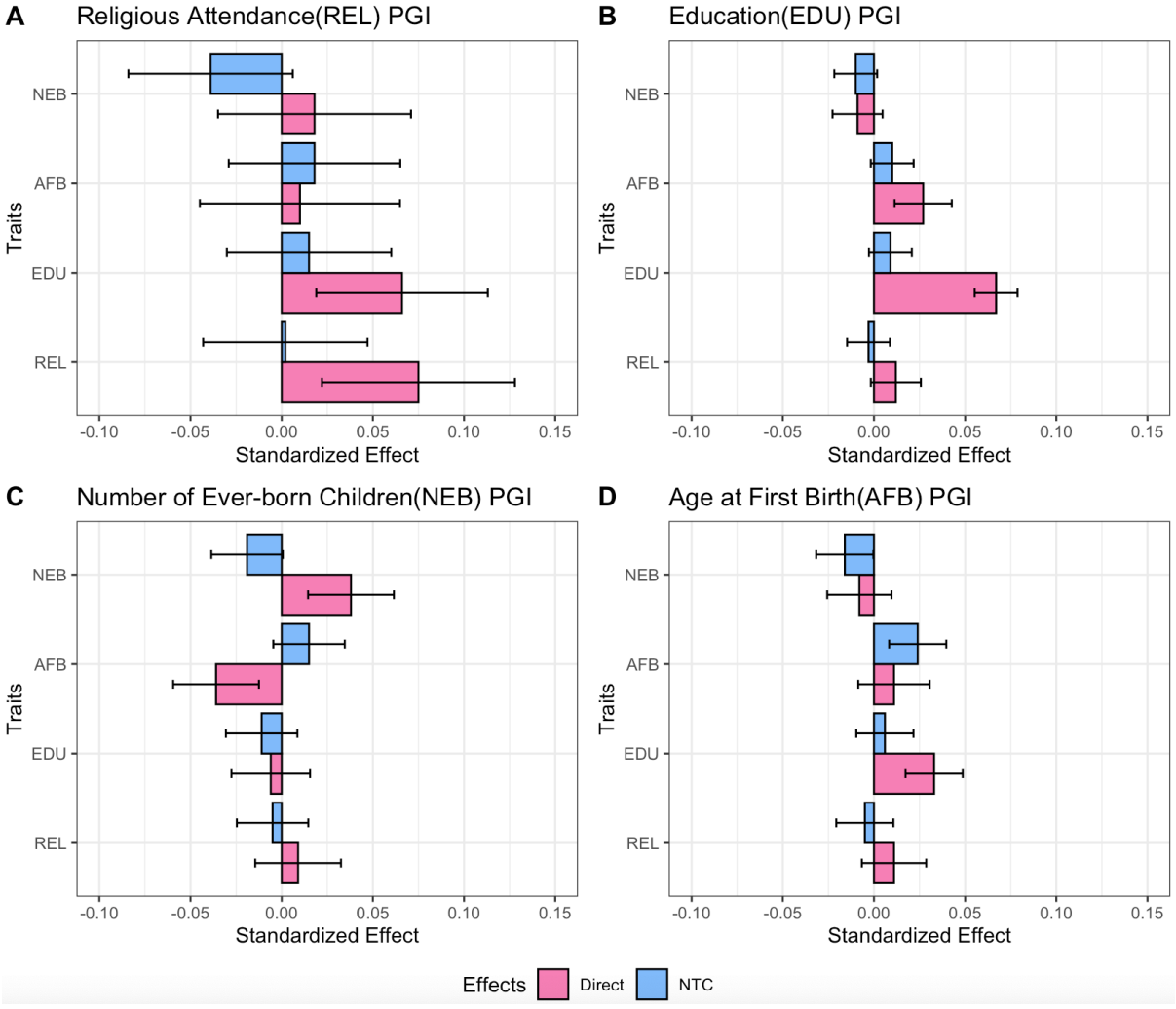


To estimate direct genetic effects, we used snipar to estimate average parental PGI and decompose the PGI effects into direct effects and average non-transmitted coefficients (NTCs). The NTCs encompass both indirect genetic effects from relatives and confounding due to population stratification and assortative mating that are not controlled for (Kong et al., 2018; Young et al., 2019, 2022). Figure 4.3.2 demonstrates the decomposed PGI effects on four traits. The standardized effect estimate is given along with the 95% confidence interval shown as error bars. Traits were adjusted for age, gender, and the top 10 genetic principal components prior to analysis.

Figure 4.3.2.A illustrates that religious attendance PGI has statistically significant direct positive effects on both education and religious attendance. However, significant direct genetic effects on religious attendance were not detected using other PGIs as predictors.

Figure 4.3.2.B demonstrates that education PGI has direct positive effects on both age at first birth and education.

Figure 4.3.2 Decomposition of PGI effects into direct effects and average non-transmitted coefficients (NTC) assuming no indirect sibling effects



In contrast, Figure 4.3.2.C shows that NEB PGI has direct positive effects on the number of everborn children but direct negative effects on age at first birth. Unlike the other three PGIs, the analysis of AFB PGI reveals a significant positive non-transmitted coefficient (NTC) for age at first birth, while the direct genetic effect on AFB is not significant. Furthermore, AFB PGI has a positive direct genetic effect on education and a negative NTC for the number of everborn children. The results from analyses assuming indirect sibling effects are displayed in Figure C.3 of the Supplementary Materials. In these analyses, we estimated the decomposition of three effects (direct, NTC, and sibling) through a joint regression approach where individuals' traits were regressed onto their own PGI, their siblings' PGI, and their imputed average parental PGI. While the assumption of no indirect sibling effects is valid for most traits and allows for more precise estimates of direct effects and average NTCs, there were statistically significant sibling effects found for REL PGI predicting religious attendance and AFB PGI predicting education, with both indirect sibling effects being negative. Our analyses did not find any direct genetic effects of religious attendance on fertility. However, we did find evidence to support the idea that the religious attendance PGI can impact fertility through the pathways that affect social traits such as education or religious attendance.

5.Discussion

Despite the decline in religious attendance over the generations, our analysis of religious assortative mating has revealed a consistent positive phenotypic correlation among spousal pairs of older Americans across birth cohorts spanning from those who were born from the 1910s to the 1970s. Regarding first-marriage pairs, a significant genotypic correlation for religious attendance was only found for females born in the 1940s and males born in the 1930s who probably chose a spouse during the social upheaval of the 1960s. However, the reasons for this finding are unclear and may require further investigation. Our analysis reveals that the self religious attendance PGI is significantly associated with spousal religious attendance, but the explained variance is relatively low compared to models using the self religious attendance phenotype. However, when we include both self and spousal PGI to predict spousal religious attendance, only the spousal PGI remains statistically significant. The stability of assortative mating for religious attendance among older American adults is demonstrated by the consistent phenotypic correlations across birth cohorts, despite the decline in religious attendance and increase in interfaith marriages (as shown in Supplementary Figure D.1). Our analysis provides limited evidence of significant religious assortative mating at the genotypic level.

The phenotypic correlation between religious attendance and fertility is significant and positive, with a small correlation coefficient of less than 0.15 for all cohorts. Genetic correlation analysis revealed a significant positive correlation between religious attendance and fertility for females and a negative correlation for males born before 1945. However, for individuals born after 1945, we did not find any significant genetic correlation. Moreover, we did not observe any genetic correlation when we analyzed both genders together. To enhance the reliability of the spousal PGI correlations, it is important to take into account possible measurement errors, including inaccurate measurements, small sample sizes, poor data quality, and limitations in the GWAS used to derive the PGI. Future researchers can re-examine spousal PGI correlations and improve the robustness of their findings by minimizing these sources of error and utilizing larger, high-quality datasets.

The opposite sign of phenotypic and genotypic associations in males born in the 1930s highlights the complexity of the relationship between genetic and environmental factors in shaping religious attendance and fertility phenotypes. This inconsistency between phenotypic and genotypic associations could be attributed to various factors. Environmental factors, such as social and cultural influences, may affect religious behavior and fertility choices, leading to a positive correlation between these two traits. However, these environmental factors may not be related to genetic factors that determine the inheritance of these traits. Furthermore,

gene-environment interactions can also play a crucial role, where genetic factors may have different effects depending on the environmental context. For instance, certain genetic variants may have a positive effect on religious attendance in one environment but a negative effect in another. Hence, the opposite sign of phenotypic and genotypic associations in males born in the 1930s demonstrates the intricate interplay between genetic and environmental factors in shaping these traits and highlights the need for further research to unravel their complex relationship.

Our regression analysis indicates that the religious attendance PGI does not significantly predict the number of everborn children (NEB), while the religious attendance phenotype can significantly predict NEB. Moreover, the NEB PGI can explain more variance in NEB than birthyear, gender, and religious attendance. Additionally, our analyses on assortative mating and differential fertility suggest that the phenotypic association may not reliably reflect the genotypic association. It is important to note that the assumption of random genetic mating may not be violated even if the phenotypic assortative mating appears positive and significant.

We found no evidence of direct or indirect genetic effects of religious attendance on age at first birth (AFB) or the number of everborn children (NEB). However, our analysis revealed

direct genetic effects of religious attendance on education, which were confirmed by both models with and without sibling indirect effects. It is important to note that the NTC estimate may be biased by population stratification and the assumption of equal weights for indirect and direct effects, making it a "naive estimate" of genetic nurture effects. To obtain a more accurate estimate, grandparental genetic effects need to be controlled for in a three-generation model and PGI needs to be constructed from within-family GWAS. Future research can further investigate the indirect effects of religious attendance PGI on fertility mediated through education. In the model without sibling indirect effects, significant direct positive genetic effects of the religious attendance PGI on religious attendance were observed. However, the sibling model revealed a negative and significant indirect sibling effect and a positive but nonsignificant NTC, suggesting that the true genetic nurture effects of religious attendance may be more complex. Further research is recommended to reevaluate the sibling model, considering the possibility of genetic nurture effects on religious attendance that can impact probands through both parents and siblings, to fully understand the underlying mechanisms.

This chapter informs our knowledge about the genetic and phenotypic landscape of religious attendance and reproduction among US older adults. The restriction of the analyses to non-Hispanic whites limits the generalizability of the study's conclusions to the wider US

population, as American society is becoming more racially and ethnically diverse (Perez & Hirschman, 2009; Vespa et al., 2018). In recent years, interracial and interethnic marriages have significantly increased, leading to more diverse families with more complex genetic ancestries (Teachman et al., 2000). This increased diversity in genetic ancestry may lead to different patterns of assortative mating and genetic correlations. As a result, the changing demographics of society may have important implications for our understanding of assortative mating and genetic correlations in future generations. To increase the external validity of their conclusions, future studies should aim to include a more diverse sample.

Recent studies have highlighted the potential biases and limitations of PGIs in capturing the true genetic effects of various traits. One major issue is population structure, where individuals from different populations may have different allele frequencies, leading to confounding effects in the estimation of genetic effects. For example, PGIs constructed using European population data may not be applicable to individuals of other ethnicities due to differences in genetic ancestry (Martin et al., 2017). Another limitation is assortative mating, where individuals with similar traits mate preferentially, leading to biases in PGIs. For instance, if highly religious individuals tend to marry each other, the PGI constructed from their offspring may overestimate the genetic effect of religious attendance. This can be

especially problematic for complex traits that are influenced by multiple genes and environmental factors.

Furthermore, this chapter presents evidence of genetic nurture, which refers to the indirect genetic effects from relatives as previously discovered (Kong et al., 2018; Wang et al., 2021). This suggests that the direct genetic effects of religious attendance may not be consistent across different environments and may be difficult to capture using proband PGIs alone. Imputing missing parental genotypes allows for increased sample size and can provide direct genetic estimates that are not achievable through unrelated individuals or sibling data alone. Gaining knowledge of direct genetic effects would largely rely on within-family designs, and increasing the sample size of genotyped closely related individuals with clear pedigrees in the future can help us better understand the direct genetic effects and gene-environment interplay. Overall, while PGIs have the potential to provide valuable insights into the genetic architecture of complex traits, it is important to consider the potential biases and limitations in their estimation. Future studies should aim to address these issues and incorporate other sources of genetic information, such as whole-genome sequencing and family-based research design, to provide a more comprehensive understanding of the genetic basis of complex traits.

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Chapter 2 Supplementary Materials

A. Religious assortative mating

Figure A.1 Proportion of weekly religious attendance across generations among spousal pairs [all marriages]

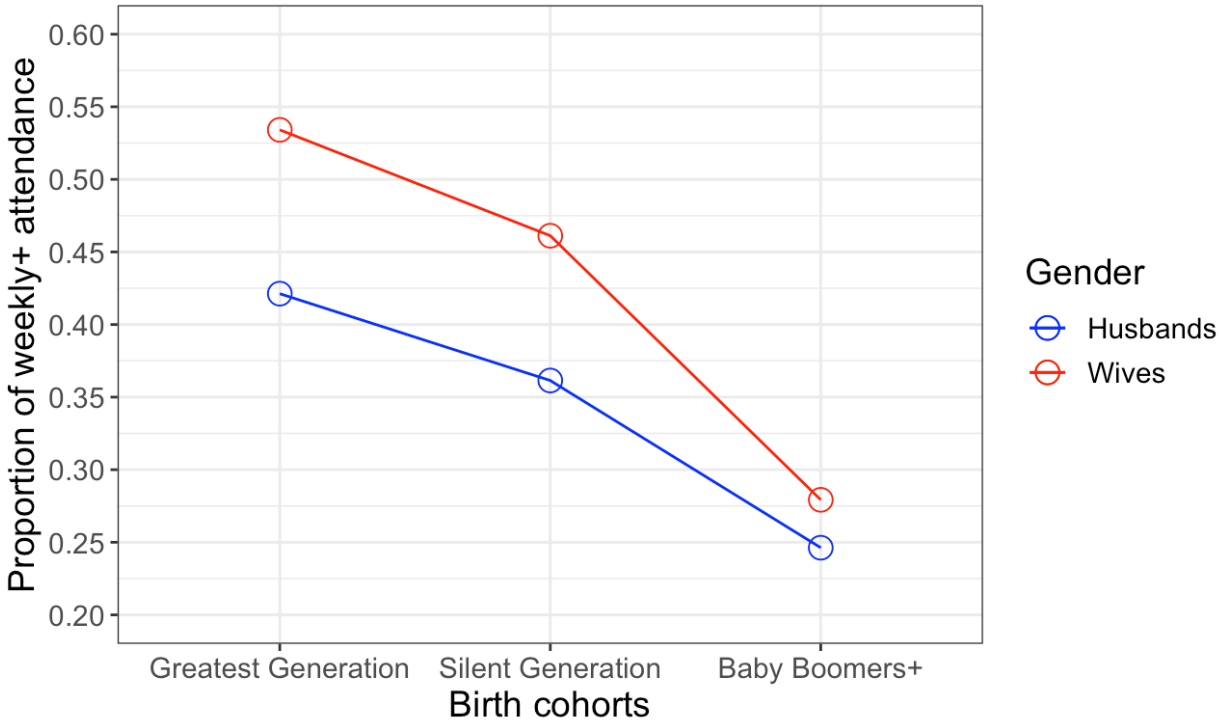


Figure A.2 Spousal correlation for religious attendance phenotypes and PGI among spousal pairs in the HRS [all marriages]

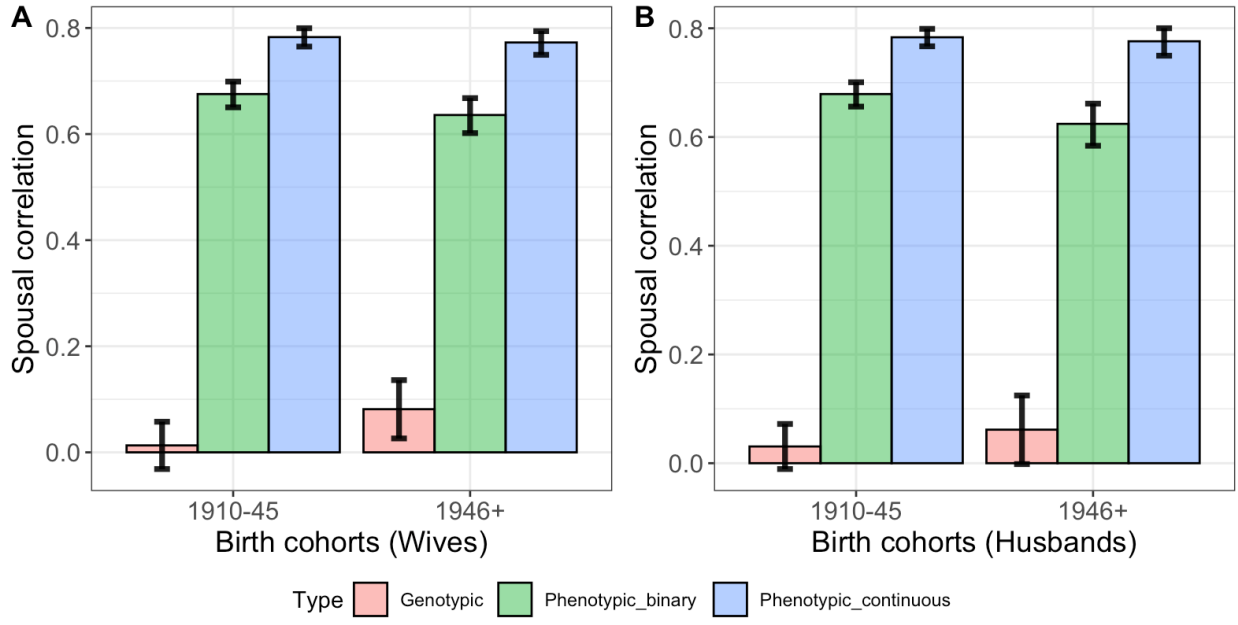


Table A.3 Spousal correlation statistics for Figure 4.1.2 and Figure A.2

Birth Cohort	Type of correlation	Marriage	Gender	Correlation	Lower CI	Upper CI	N
1910-45	Genotypic	First	Female	0.025	-0.026	0.076	1473
1910-45	Phenotypic_binary	First	Female	0.665	0.635	0.692	1473
1910-45	Phenotypic_continuous	First	Female	0.777	0.756	0.797	1473
1946+	Genotypic	First	Female	0.060	-0.005	0.126	886
1946+	Phenotypic_binary	First	Female	0.620	0.578	0.659	886
1946+	Phenotypic_continuous	First	Female	0.783	0.756	0.807	886
1910-45	Genotypic	First	Male	0.040	-0.008	0.088	1655
1910-45	Phenotypic_binary	First	Male	0.656	0.628	0.683	1655
1910-45	Phenotypic_continuous	First	Male	0.772	0.752	0.791	1655
1946+	Genotypic	First	Male	0.035	-0.039	0.108	704
1946+	Phenotypic_binary	First	Male	0.638	0.591	0.679	704
1946+	Phenotypic_continuous	First	Male	0.802	0.774	0.827	704
1910-45	Genotypic	All	Female	0.013	-0.032	0.058	1932
1910-45	Phenotypic_binary	All	Female	0.675	0.650	0.699	1932
1910-45	Phenotypic_continuous	All	Female	0.783	0.765	0.800	1932
1946+	Genotypic	All	Female	0.081	0.026	0.136	1255
1946+	Phenotypic_binary	All	Female	0.636	0.602	0.668	1255
1946+	Phenotypic_continuous	All	Female	0.773	0.749	0.794	1255
1910-45	Genotypic	All	Male	0.031	-0.011	0.072	2229
1910-45	Phenotypic_binary	All	Male	0.679	0.656	0.701	2229
1910-45	Phenotypic_continuous	All	Male	0.783	0.767	0.799	2229
1946+	Genotypic	All	Male	0.062	-0.002	0.125	958
1946+	Phenotypic_binary	All	Male	0.624	0.584	0.661	958
1946+	Phenotypic_continuous	All	Male	0.776	0.750	0.800	958

Figure A.4 Spousal correlation for religious attendance phenotypes and PGI among spousal pairs by more specific cohorts in the HRS [first marriages]

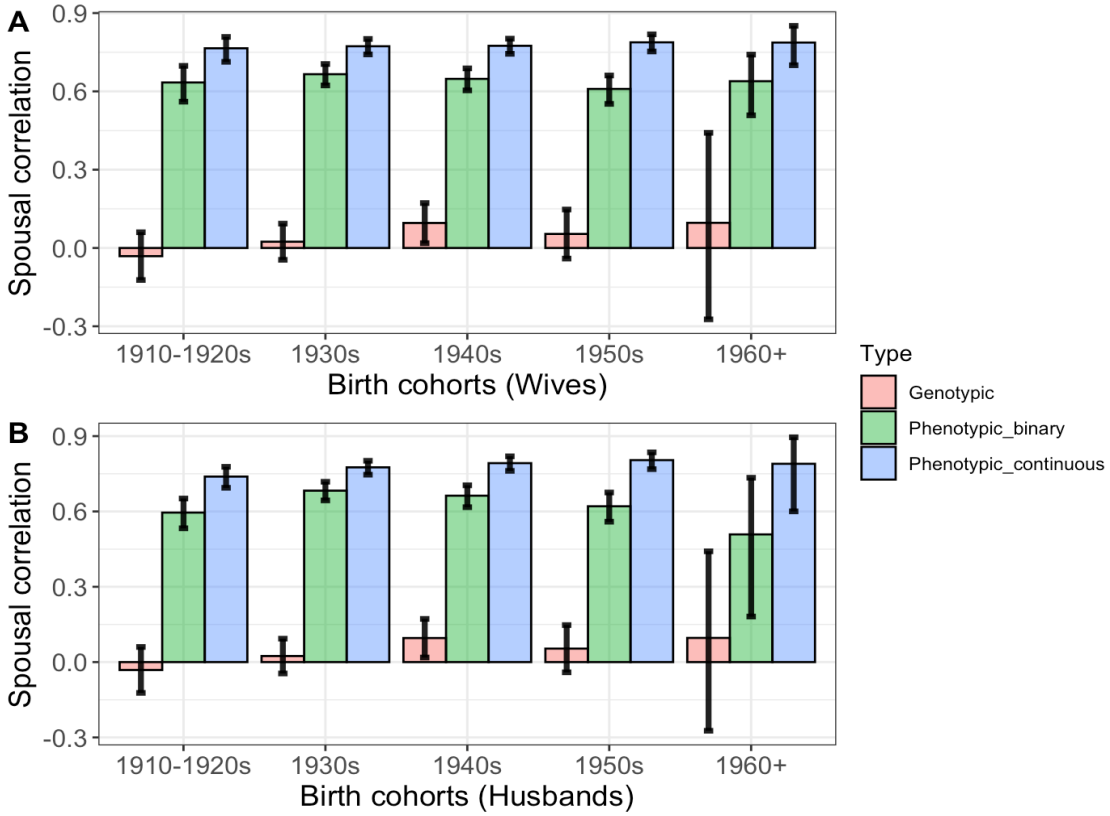


Figure A.5 Spousal correlation for religious attendance phenotypes and PGI among spousal pairs by more specific cohorts in the HRS [all marriages]

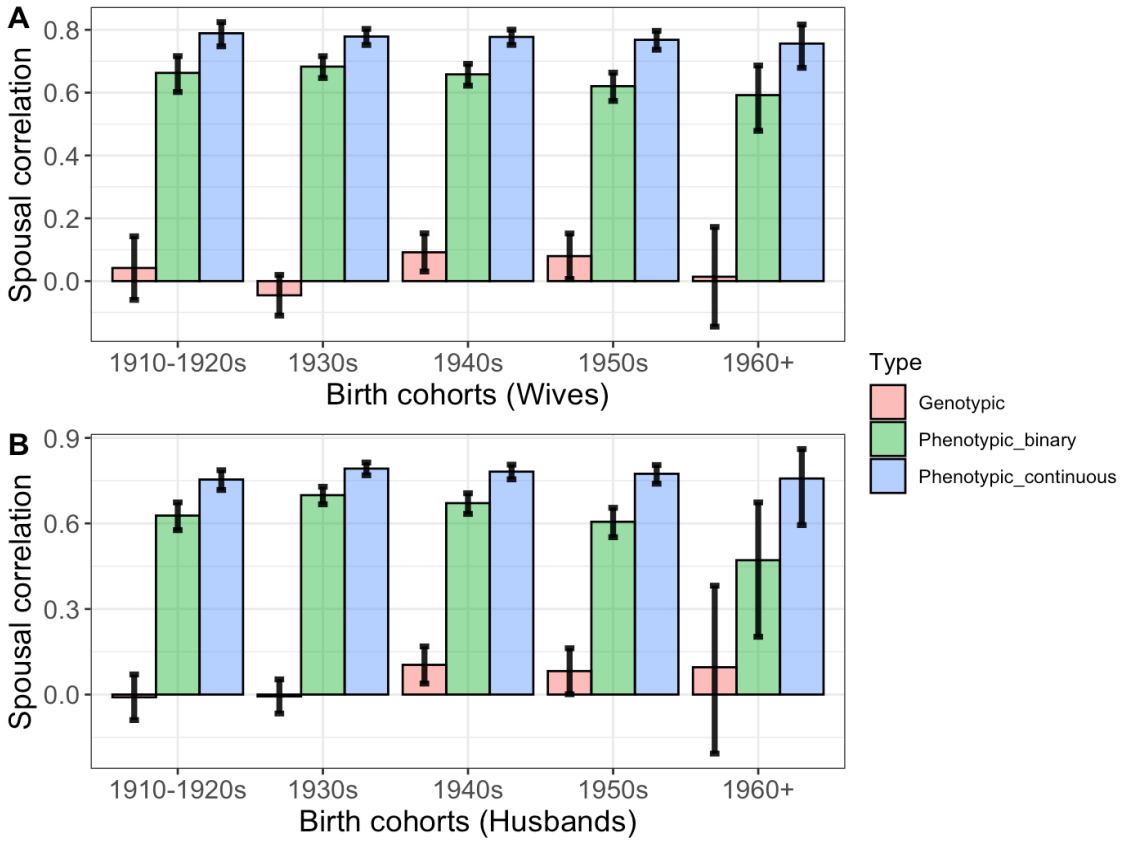


Table A.6 Predicting wives' religious attendance among spousal pairs in the HRS [all marriages]

	Wives Model1	Model2	Model3	Model4	Model5	Model6	Model7
(Intercept)	0.739***	0.732***	0.733***	0.726***	0.727***	0.219***	0.219***
	(0.067)	(0.067)	(0.067)	(0.067)	(0.067)	(0.046)	(0.045)
m_birthyear	−0.183***	−0.181***	−0.181***	−0.180***	−0.180***	−0.057***	−0.057***
	(0.016)	(0.016)	(0.016)	(0.016)	(0.016)	(0.011)	(0.011)
m_REL_PGI		0.089***		0.086***	0.048		0.007
		(0.018)		(0.018)	(0.066)		(0.011)
f_REL_PGI			0.093***	0.090***	0.089***		0.038**
			(0.018)	(0.018)	(0.018)		(0.012)
m_birthyear × m_REL_PGI					0.010		
					(0.016)		
m_REL_stdz						0.753***	0.749***
						(0.043)	(0.043)
m_birthyear × m_REL_stdz						0.007	0.008
						(0.011)	(0.011)
Num.Obs.	3187	3187	3187	3187	3187	3187	3187
R2	0.035	0.042	0.043	0.050	0.050	0.620	0.621
R2 Adj.	0.034	0.042	0.042	0.049	0.049	0.619	0.620
AIC	9063.9	9040.1	9038.6	9016.7	9018.3	6099.7	6091.9
BIC	9082.1	9064.3	9062.9	9047.0	9054.7	6130.1	6134.4
RMSE	1.00	1.00	1.00	0.99	0.99	0.63	0.63

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Model 1 uses spousal birthyear as a single predictor, which is highly correlated with self-birthyear with a correlation coefficient of 0.86 and a 95% confidence interval of [-0.855, -0.873].

Table A.7 Predicting husbands' religious attendance among spousal pairs in the HRS [all marriages]

	Husbands Model1	Model2	Model3	Model4	Model5	Model6	Model7
(Intercept)	0.820***	0.818***	0.805***	0.804***	0.805***	0.134**	0.131**
	(0.072)	(0.072)	(0.072)	(0.072)	(0.072)	(0.047)	(0.047)
f_birthyear	−0.185***	−0.184***	−0.182***	−0.182***	−0.182***	−0.028*	−0.028*
	(0.016)	(0.016)	(0.016)	(0.016)	(0.016)	(0.011)	(0.011)
f_REL_PGI		0.073***		0.069***	0.199**		−0.003
		(0.018)		(0.018)	(0.072)		(0.012)
m_REL_PGI			0.101***	0.098***	0.099***		0.035**
			(0.017)	(0.017)	(0.017)		(0.011)
f_REL_PGI × f_birthyear					−0.031+		
					(0.016)		
f_REL_stdz						0.860***	0.859***
						(0.045)	(0.045)
f_birthyear × f_REL_stdz						−0.021+	−0.021*
						(0.011)	(0.011)
Num.Obs.	3187	3187	3187	3187	3187	3187	3187
R2	0.037	0.042	0.047	0.052	0.053	0.617	0.619
R2 Adj.	0.037	0.042	0.047	0.051	0.052	0.617	0.618
AIC	9000.4	8985.5	8968.9	8955.7	8954.4	6062.6	6056.3
BIC	9018.6	9009.8	8993.1	8986.0	8990.8	6092.9	6098.8
RMSE	0.99	0.99	0.99	0.98	0.98	0.63	0.62

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Table A.8 Predicting wives' religious attendance [binary measurement] among spousal pairs in the HRS using logistic regression [first marriages]

	Model1	Model2	Model3	Model4	Model5	Model6	Model7
(Intercept)	1.394***	1.391***	1.395***	1.393***	1.394***	−0.080	−0.070
	(0.172)	(0.172)	(0.172)	(0.172)	(0.173)	(0.262)	(0.263)
m_birthyear	−0.420***	−0.421***	−0.421***	−0.422***	−0.422***	−0.352***	−0.354***
	(0.043)	(0.043)	(0.043)	(0.043)	(0.043)	(0.066)	(0.067)
f_PC1	−19.632**	−19.391**	−19.023**	−18.780**	−18.760**	−9.935	−9.665
	(6.137)	(6.136)	(6.195)	(6.191)	(6.193)	(7.768)	(7.812)
f_PC2	−10.132*	−10.480*	−8.452+	−8.811+	−8.819+	−8.140	−6.550
	(4.611)	(4.618)	(4.649)	(4.655)	(4.655)	(6.017)	(6.043)
f_PC3	7.068	7.485	10.076	10.436	10.429	11.034	13.087
	(6.778)	(6.774)	(6.855)	(6.848)	(6.849)	(8.362)	(8.421)
f_PC4	6.756	7.090	5.538	5.888	5.876	18.973*	17.856+
	(7.858)	(7.852)	(7.908)	(7.898)	(7.900)	(9.516)	(9.555)
f_PC5	16.644*	17.102*	16.352*	16.810*	16.768*	23.914**	23.541**
	(7.236)	(7.241)	(7.279)	(7.283)	(7.290)	(9.019)	(9.020)
f_PC6	−28.846***	−29.368***	−30.560***	−31.035***	−31.039***	−26.014***	−27.256***
	(5.889)	(5.895)	(5.950)	(5.953)	(5.953)	(7.457)	(7.534)
f_PC7	−4.465	−4.701	−3.866	−4.119	−4.116	−1.843	−1.185
	(4.859)	(4.866)	(4.881)	(4.887)	(4.886)	(6.454)	(6.467)
f_PC8	−25.631**	−25.986**	−25.616*	−25.959**	−25.911**	−24.938*	−24.721*
	(9.936)	(9.949)	(9.965)	(9.976)	(9.982)	(12.553)	(12.546)
f_PC9	−9.617*	−9.170*	−9.028+	−8.604+	−8.574+	−0.852	−0.518
	(4.645)	(4.655)	(4.664)	(4.673)	(4.678)	(6.062)	(6.080)
f_PC10	−7.990+	−7.749+	−7.633+	−7.397	−7.391	−3.245	−3.083
	(4.522)	(4.528)	(4.537)	(4.542)	(4.542)	(5.978)	(5.989)
m_REL_PGI		0.114**		0.108*	0.086		−0.044
		(0.043)		(0.043)	(0.169)		(0.056)
f_REL_PGI			0.197***	0.193***	0.193***		0.149*
			(0.044)	(0.045)	(0.045)		(0.058)
m_REL_PGI × m_birthyear					0.006		
					(0.042)		
m_REL_weekly						3.411***	3.401***
						(0.495)	(0.497)
m_birthyear × m_REL_weekly						−0.016	−0.013
						(0.122)	(0.123)
Num.Obs.	2359	2359	2359	2359	2359	2359	2359
AIC	3106.7	3101.7	3088.9	3084.6	3086.6	2060.4	2057.3
BIC	3175.9	3176.7	3163.9	3165.4	3173.1	2141.1	2149.6
Log.Lik.	−1541.373	−1537.859	−1531.454	−1528.320	−1528.311	−1016.186	−1012.674
F	12.267	11.749	12.586	12.025	11.164	59.136	51.142
RMSE	0.48	0.48	0.48	0.48	0.48	0.36	0.36

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Table A.9 Predicting husbands' religious attendance [binary measurement] among spousal pairs in the HRS using logistic regression [first marriages]

	Model1	Model2	Model3	Model4	Model5	Model6	Model7
(Intercept)	0.983***	0.990***	0.979***	0.985***	0.971***	−2.091***	−2.098***
	(0.181)	(0.182)	(0.182)	(0.183)	(0.183)	(0.425)	(0.426)
f_birthyear	−0.373***	−0.375***	−0.375***	−0.378***	−0.375***	−0.071	−0.076
	(0.043)	(0.043)	(0.043)	(0.043)	(0.043)	(0.095)	(0.095)
m_PC1	−34.938***	−34.637***	−33.569***	−33.249***	−33.482***	−26.724**	−24.859**
	(7.158)	(7.191)	(7.189)	(7.217)	(7.236)	(8.617)	(8.701)
m_PC2	4.279	3.976	5.928	5.576	6.019	3.765	5.771
	(4.636)	(4.648)	(4.673)	(4.684)	(4.694)	(6.064)	(6.145)
m_PC3	0.077	1.189	3.591	4.574	4.869	7.373	11.902
	(5.873)	(5.859)	(5.955)	(5.940)	(5.934)	(7.554)	(7.715)
m_PC4	0.369	1.102	−0.230	0.512	0.265	−2.013	−3.242
	(6.444)	(6.415)	(6.482)	(6.454)	(6.441)	(8.378)	(8.507)
m_PC5	−1.041	0.104	−1.215	−0.104	−0.066	−6.033	−5.967
	(6.028)	(6.006)	(6.061)	(6.040)	(6.030)	(7.818)	(7.914)
m_PC6	−28.027***	−29.137***	−28.925***	−29.938***	−30.295***	−23.253**	−24.938**
	(6.886)	(6.930)	(6.917)	(6.956)	(6.975)	(8.288)	(8.380)
m_PC7	−1.179	−0.992	−1.184	−0.982	−0.736	−5.355	−5.196
	(4.774)	(4.790)	(4.799)	(4.814)	(4.818)	(6.363)	(6.420)
m_PC8	−4.868	−5.298	−5.374	−5.745	−5.273	−6.187	−7.723
	(8.551)	(8.570)	(8.564)	(8.585)	(8.560)	(11.250)	(11.324)
m_PC9	0.705	1.190	1.486	1.893	1.997	−3.025	−1.793
	(4.785)	(4.798)	(4.809)	(4.821)	(4.824)	(6.313)	(6.366)
m_PC10	8.162+	9.068*	7.317	8.197+	8.158+	3.557	3.290
	(4.535)	(4.561)	(4.561)	(4.586)	(4.589)	(5.953)	(5.999)
f_REL_PGI		0.182***		0.176***	0.530**		0.072
		(0.045)		(0.045)	(0.189)		(0.059)
m_REL_PGI			0.209***	0.204***	0.208***		0.266***
			(0.045)	(0.045)	(0.045)		(0.060)
f_REL_PGI × f_birthyear					−0.086+		
					(0.045)		
f_REL_weekly						3.626***	3.619***
						(0.514)	(0.516)
f_birthyear × f_REL_weekly						−0.070	−0.065
						(0.118)	(0.119)
Num.Obs.	2359	2359	2359	2359	2359	2359	2359
AIC	3007.2	2992.4	2987.3	2973.7	2972.0	1976.7	1958.5
BIC	3076.4	3067.4	3062.3	3054.5	3058.5	2057.4	2050.8
Log.Lik.	−1491.589	−1483.203	−1480.662	−1472.864	−1470.990	−974.343	−963.266
F	9.774	10.150	10.509	10.704	10.154	59.811	51.361
RMSE	0.47	0.47	0.47	0.47	0.47	0.36	0.36

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Table A.10 Predicting wives' religious attendance [binary measurement] among spousal pairs in the HRS using logistic regression [all marriages]

	All Model1	Model2	Model3	Model4	Model5	Model6	Model7
(Intercept)	1.256***	1.251***	1.254***	1.249***	1.250***	−0.331	−0.326
	(0.148)	(0.148)	(0.148)	(0.148)	(0.148)	(0.231)	(0.232)
m_birthyear	−0.414***	−0.414***	−0.414***	−0.413***	−0.414***	−0.321***	−0.323***
	(0.037)	(0.037)	(0.037)	(0.037)	(0.037)	(0.058)	(0.058)
f_PC1	−23.418***	−22.733***	−22.530***	−21.857***	−21.849***	−13.093+	−12.249+
	(5.557)	(5.556)	(5.594)	(5.591)	(5.591)	(7.146)	(7.177)
f_PC2	−5.109	−5.543	−3.916	−4.363	−4.365	−0.061	1.163
	(3.981)	(3.990)	(4.004)	(4.012)	(4.012)	(5.279)	(5.299)
f_PC3	−0.449	0.512	2.601	3.465	3.461	6.278	9.219
	(5.854)	(5.842)	(5.910)	(5.897)	(5.898)	(7.138)	(7.210)
f_PC4	0.824	1.451	0.167	0.794	0.787	14.088+	13.391+
	(6.744)	(6.720)	(6.766)	(6.740)	(6.741)	(8.016)	(8.047)
f_PC5	9.565	10.281+	9.709	10.420+	10.392+	16.971*	17.021*
	(6.164)	(6.161)	(6.186)	(6.183)	(6.188)	(7.582)	(7.597)
f_PC6	−25.738***	−26.300***	−26.955***	−27.488***	−27.493***	−25.329***	−26.643***
	(5.339)	(5.343)	(5.377)	(5.379)	(5.379)	(6.893)	(6.940)
f_PC7	−3.890	−4.271	−3.520	−3.916	−3.916	0.246	0.661
	(4.117)	(4.128)	(4.130)	(4.141)	(4.140)	(5.493)	(5.502)
f_PC8	−12.507	−13.035	−13.091	−13.585	−13.559	−11.957	−12.517
	(8.277)	(8.278)	(8.296)	(8.296)	(8.299)	(10.254)	(10.269)
f_PC9	−6.910+	−6.377	−6.701+	−6.164	−6.138	0.790	1.017
	(4.004)	(4.015)	(4.016)	(4.027)	(4.032)	(5.286)	(5.306)
f_PC10	−6.662+	−6.603+	−6.730+	−6.654+	−6.655+	−4.538	−4.624
	(3.899)	(3.909)	(3.909)	(3.918)	(3.918)	(5.221)	(5.230)
m_REL_PGI		0.158***		0.154***	0.136		0.002
		(0.037)		(0.037)	(0.145)		(0.049)
f_REL_PGI			0.180***	0.175***	0.175***		0.176***
			(0.038)	(0.039)	(0.039)		(0.051)
m_REL_PGI × m_birthyear					0.005		
					(0.037)		
m_REL_weekly						3.807***	3.800***
						(0.436)	(0.438)
m_birthyear × m_REL_weekly						−0.095	−0.094
						(0.107)	(0.108)
Num.Obs.	3187	3187	3187	3187	3187	3187	3187
AIC	4168.5	4152.1	4148.4	4133.2	4135.2	2705.0	2697.1
BIC	4241.3	4231.0	4227.2	4218.1	4226.2	2789.9	2794.2
Log.Lik.	−2072.239	−2063.053	−2061.176	−2052.595	−2052.587	−1338.486	−1332.566
F	14.812	14.925	15.120	15.090	14.009	80.789	69.757
RMSE	0.48	0.48	0.48	0.48	0.48	0.36	0.36

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Table A.11 Predicting husbands' religious attendance [binary measurement] among spousal pairs in the HRS using logistic regression [all marriages]

	All Model1	Model2	Model3	Model4	Model5	Model6	Model7
(Intercept)	1.005***	1.009***	0.988***	0.993***	0.990***	−2.111***	−2.138***
	(0.159)	(0.159)	(0.160)	(0.160)	(0.160)	(0.369)	(0.370)
f_birthyear	−0.389***	−0.391***	−0.388***	−0.390***	−0.389***	−0.076	−0.073
	(0.037)	(0.037)	(0.037)	(0.038)	(0.038)	(0.082)	(0.082)
m_PC1	−31.461***	−31.357***	−30.230***	−30.118***	−30.273***	−23.576**	−21.968**
	(6.098)	(6.117)	(6.156)	(6.172)	(6.186)	(7.486)	(7.549)
m_PC2	4.172	4.107	5.773	5.665	5.972	3.856	5.673
	(3.970)	(3.975)	(4.004)	(4.007)	(4.015)	(5.238)	(5.290)
m_PC3	−0.429	0.023	3.464	3.814	3.858	2.542	6.780
	(4.909)	(4.902)	(4.987)	(4.980)	(4.975)	(6.411)	(6.502)
m_PC4	5.917	6.390	5.052	5.503	5.263	2.672	1.613
	(5.383)	(5.374)	(5.420)	(5.413)	(5.399)	(7.049)	(7.079)
m_PC5	2.316	3.095	1.686	2.412	2.449	0.007	−0.432
	(5.137)	(5.133)	(5.173)	(5.170)	(5.163)	(6.813)	(6.846)
m_PC6	−26.033***	−26.621***	−26.915***	−27.414***	−27.680***	−20.231**	−20.870**
	(5.943)	(5.972)	(6.003)	(6.027)	(6.040)	(7.298)	(7.369)
m_PC7	1.225	1.376	1.438	1.579	1.791	1.554	1.952
	(4.086)	(4.093)	(4.114)	(4.121)	(4.125)	(5.488)	(5.540)
m_PC8	−4.540	−4.884	−4.719	−4.996	−4.565	−5.396	−6.022
	(7.289)	(7.302)	(7.328)	(7.346)	(7.331)	(9.672)	(9.661)
m_PC9	1.387	1.757	2.500	2.813	2.903	−0.328	0.999
	(4.106)	(4.112)	(4.132)	(4.138)	(4.142)	(5.492)	(5.536)
m_PC10	5.488	5.864	4.728	5.091	5.039	0.586	−0.063
	(3.887)	(3.898)	(3.911)	(3.921)	(3.924)	(5.171)	(5.190)
f_REL_PGI		0.141***		0.134***	0.459**		0.009
		(0.039)		(0.039)	(0.165)		(0.052)
m_REL_PGI			0.233***	0.229***	0.232***		0.248***
			(0.039)	(0.039)	(0.039)		(0.052)
f_REL_PGI × f_birthyear					−0.078*		
					(0.038)		
f_REL_weekly						3.779***	3.791***
						(0.451)	(0.453)
f_birthyear × f_REL_weekly						−0.089	−0.091
						(0.103)	(0.103)
Num.Obs.	3187	3187	3187	3187	3187	3187	3187
AIC	4003.0	3991.5	3969.0	3959.0	3956.9	2572.6	2553.8
BIC	4075.8	4070.4	4047.9	4043.9	4047.9	2657.5	2650.9
Log.Lik.	−1989.490	−1982.757	−1971.500	−1965.499	−1963.430	−1272.305	−1260.903
F	13.208	13.053	14.645	14.267	13.499	82.748	71.166
RMSE	0.47	0.47	0.46	0.46	0.46	0.35	0.35

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

B. Differential fertility

Table B.1 HRS descriptive statistics, non-Hispanic whites (n = 10,472) with both genotypic data and valid phenoypic responses by gender

	Female sample (n = 6,015)			Male sample (n = 4,457)		
Variables	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**
Birthyear	1939.68	11.75	[1905, 1979]	1939.11	10.95	[1907, 1975]
REL PGI	0.00	0.99	[-3.89, 3.49]	0.00	1.01	[-4.45, 3.98]
NEBF/NEBM PGI	0.00	1.00	[-5.00, 3.98]	0.00	1.00	[-3.11, 4.98]
Religious attendance [times/year]	33.59	28.94	[0, 91]	28.33	28.94	[0, 90]
Religious attendance [>=weekly]	0.40	binary	[0, 1]	0.33	binary	[0, 1]
Number of Everborn Children (NEB)	2.53	1.63	[0, 11]	2.43	1.60	[0, 11]

Table B.2 Genotypic and phenotypic correlations between religious attendance (REL) and number of everborn children (NEB) among non-Hispanic whites in the HRS for Figure 4.2.1

Cohort	Type	Gender	Estimate	Lower CI	Upper CI	N
1910-45	Genotypic	Combined	0.018	-0.005	0.041	7098
1910-45	Phenotypic	Combined	0.092	0.069	0.115	7098
1946+	Genotypic	Combined	0.014	-0.020	0.047	3374
1946+	Phenotypic	Combined	0.092	0.059	0.125	3374
1910-45	Genotypic	Female	0.038	0.007	0.069	4023
1910-45	Phenotypic	Female	0.053	0.022	0.084	4023
1946+	Genotypic	Female	0.016	-0.028	0.060	1992
1946+	Phenotypic	Female	0.078	0.035	0.122	1992
1910-45	Genotypic	Male	-0.052	-0.087	-0.016	3075
1910-45	Phenotypic	Male	0.136	0.101	0.170	3075
1946+	Genotypic	Male	0.034	-0.018	0.087	1382
1946+	Phenotypic	Male	0.109	0.056	0.161	1382

Figure B.3 Genotypic and phenotypic correlations between religious attendance (REL) and number of everborn children (NEB) with more specific birth cohorts

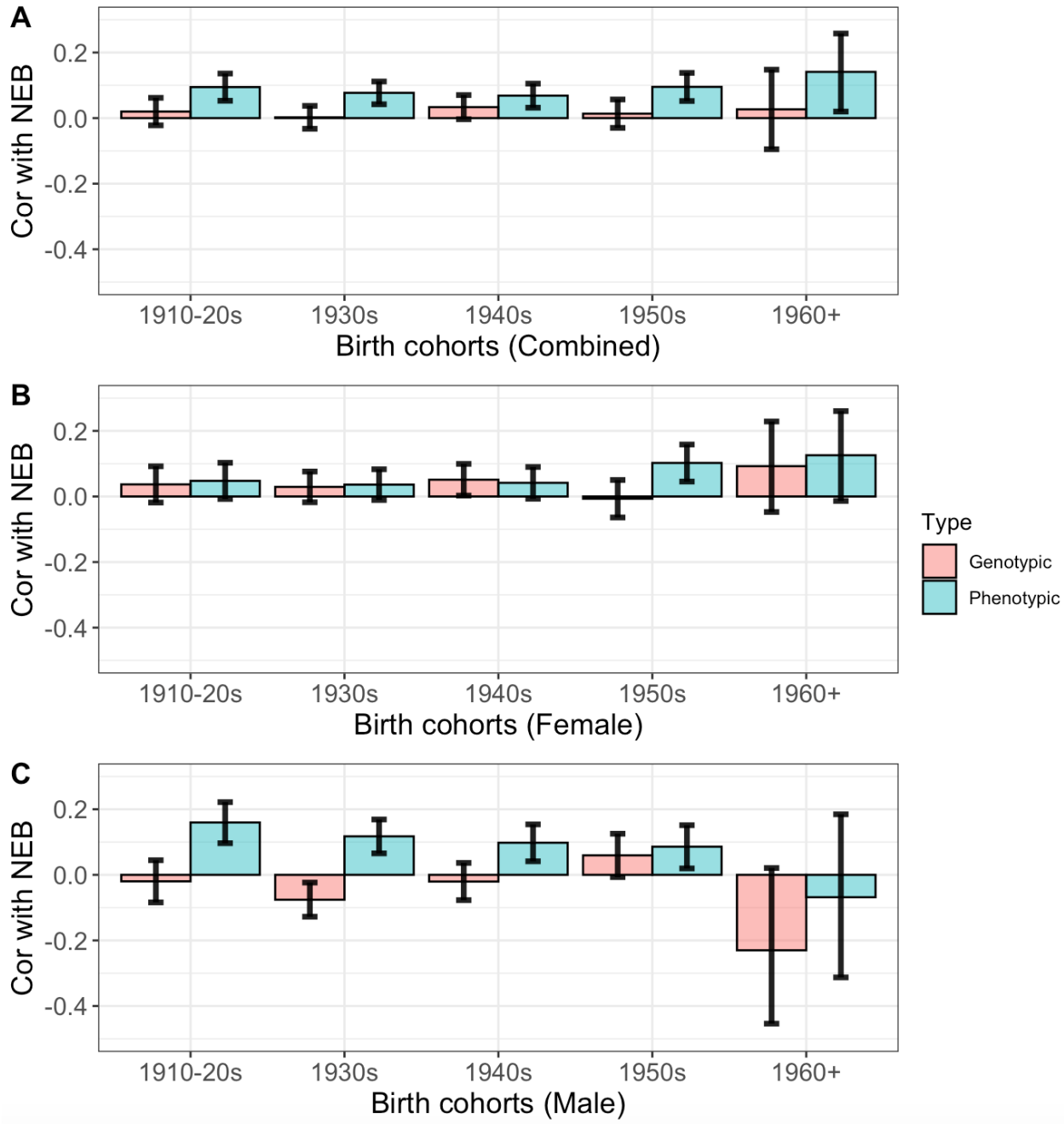


Table B.4 Utilizing genotypic data and Poisson regression models to predict the number of children everborn (NEB) for non-Hispanic whites in the HRS

	Model1	Model2	Model3	Model4	Model5	Model6	Model7
(Intercept)	1.450***	1.450***	1.454***	1.454***	1.416***	1.418***	1.420***
	(0.022)	(0.022)	(0.022)	(0.022)	(0.023)	(0.023)	(0.023)
Birthyear	−0.136***	−0.136***	−0.142***	−0.143***	−0.134***	−0.134***	−0.135***
	(0.005)	(0.005)	(0.005)	(0.005)	(0.006)	(0.006)	(0.006)
GenderMale	−0.042***	−0.042***	−0.039**	−0.039**	−0.029*	−0.029*	−0.031*
	(0.013)	(0.013)	(0.013)	(0.013)	(0.013)	(0.013)	(0.013)
PC1	−4.286***	−4.297***	3.986***	3.978***	3.973***	3.944***	3.974***
	(0.859)	(0.859)	(0.897)	(0.898)	(0.898)	(0.898)	(0.898)
PC2	−1.222+	−1.242+	0.913	0.900	0.821	0.851	0.835
	(0.704)	(0.706)	(0.706)	(0.708)	(0.709)	(0.709)	(0.709)
PC3	−0.334	−0.372	−0.935	−0.960	−1.113	−1.120	−0.996
	(1.403)	(1.407)	(1.406)	(1.410)	(1.411)	(1.411)	(1.411)
PC4	−1.823	−1.818	−0.440	−0.437	−0.495	−0.511	−0.425
	(1.689)	(1.689)	(1.692)	(1.692)	(1.692)	(1.692)	(1.692)
PC5	−0.084	−0.083	−4.483**	−4.482**	−4.536**	−4.556**	−4.438**
	(1.401)	(1.401)	(1.412)	(1.412)	(1.412)	(1.412)	(1.412)
PC6	−2.438**	−2.431**	−1.409+	−1.404+	−1.365+	−1.365+	−1.369+
	(0.755)	(0.756)	(0.756)	(0.757)	(0.757)	(0.757)	(0.757)
PC7	0.510	0.503	−0.637	−0.642	−0.618	−0.623	−0.614
	(0.726)	(0.727)	(0.727)	(0.727)	(0.727)	(0.727)	(0.727)
PC8	−0.373	−0.382	−1.635	−1.640	−1.680	−1.589	−1.610
	(1.716)	(1.716)	(1.712)	(1.712)	(1.711)	(1.712)	(1.711)
PC9	−1.594*	−1.603*	−1.292+	−1.297+	−1.318+	−1.289+	−1.311+
	(0.707)	(0.708)	(0.706)	(0.707)	(0.707)	(0.707)	(0.707)
PC10	0.107	0.110	0.606	0.607	0.607	0.614	0.565
	(0.657)	(0.657)	(0.658)	(0.658)	(0.658)	(0.658)	(0.658)
REL_PGI		−0.002		−0.001	−0.006	−0.006	−0.007
		(0.006)		(0.006)	(0.006)	(0.006)	(0.006)
NEBC_PGI			0.219***	0.219***	0.218***	0.218***	0.218***
			(0.007)	(0.007)	(0.007)	(0.007)	(0.007)
REL_stdz					0.054***	0.015	0.037***
					(0.006)	(0.022)	(0.008)
REL_stdz × Birthyear						0.010+	
						(0.006)	
REL_stdz × GenderMale							0.041***
							(0.012)
Num.Obs.	10 472	10 472	10 472	10 472	10 472	10 472	10 472
AIC	38 168.7	38 170.6	37 117.4	37 119.3	37 047.2	37 045.9	37 038.2
BIC	38 263.0	38 272.1	37 219.0	37 228.2	37 163.3	37 169.2	37 161.6
Log.Lik.	−19 071.338	−19 071.276	−18 544.686	−18 544.659	−18 507.596	−18 505.927	−18 502.096
F	56.294	51.972	133.472	123.943	120.573	112.887	113.742
RMSE	1.57	1.57	1.48	1.48	1.48	1.48	1.48

+ $p < 0.1$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table B.5 Predicting the standardized number of children everborn (NEB) for non-Hispanic white females in the HRS with genotypic data

	Female Model1	Model2	Model3	Model4	Model5	Model6
(Intercept)	0.802***	0.802***	0.830***	0.830***	0.791***	0.792***
	(0.048)	(0.048)	(0.045)	(0.045)	(0.046)	(0.046)
Birthyear	−0.196***	−0.196***	−0.205***	−0.205***	−0.196***	−0.196***
	(0.011)	(0.011)	(0.010)	(0.010)	(0.011)	(0.011)
REL_PGI		0.004		−0.007	−0.011	−0.010
		(0.013)		(0.012)	(0.012)	(0.012)
NEBF_PGI			0.339***	0.340***	0.338***	0.338***
			(0.013)	(0.013)	(0.013)	(0.013)
REL_stdz					0.054***	0.030
					(0.012)	(0.049)
Birthyear × REL_stdz						0.006
						(0.011)
Num.Obs.	6015	6015	6015	6015	6015	6015
R2	0.053	0.053	0.174	0.174	0.177	0.177
R2 Adj.	0.052	0.052	0.174	0.173	0.176	0.176
AIC	16 820.4	16 822.3	15 998.8	16 000.5	15 982.8	15 984.5
BIC	16 840.5	16 849.1	16 025.6	16 034.0	16 023.1	16 031.4
RMSE	0.98	0.98	0.91	0.91	0.91	0.91

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Table B.6 Predicting the standardized number of children everborn (NEB) for non-Hispanic white males in the HRS with genotypic data

	Male Model1	Model2	Model3	Model4	Model5	Model6
(Intercept)	0.857***	0.858***	0.909***	0.909***	0.858***	0.855***
	(0.057)	(0.057)	(0.051)	(0.051)	(0.051)	(0.052)
Birthyear	−0.227***	−0.228***	−0.239***	−0.239***	−0.224***	−0.222***
	(0.014)	(0.014)	(0.013)	(0.013)	(0.013)	(0.013)
REL_PGI		−0.014		−0.002	−0.013	−0.012
		(0.014)		(0.013)	(0.013)	(0.013)
NEBM_PGI			0.404***	0.404***	0.402***	0.402***
			(0.013)	(0.013)	(0.013)	(0.013)
REL_stdz					0.107***	0.072
					(0.013)	(0.054)
Birthyear × REL_stdz						0.009
						(0.014)
Num.Obs.	4457	4457	4457	4457	4457	4457
R2	0.063	0.063	0.271	0.271	0.282	0.282
R2 Adj.	0.063	0.063	0.271	0.270	0.281	0.281
AIC	12 285.1	12 286.2	11 169.3	11 171.2	11 105.3	11 106.7
BIC	12 304.3	12 311.8	11 194.9	11 203.2	11 143.7	11 151.5
RMSE	0.96	0.96	0.85	0.85	0.84	0.84

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

C. Direct genetic effects

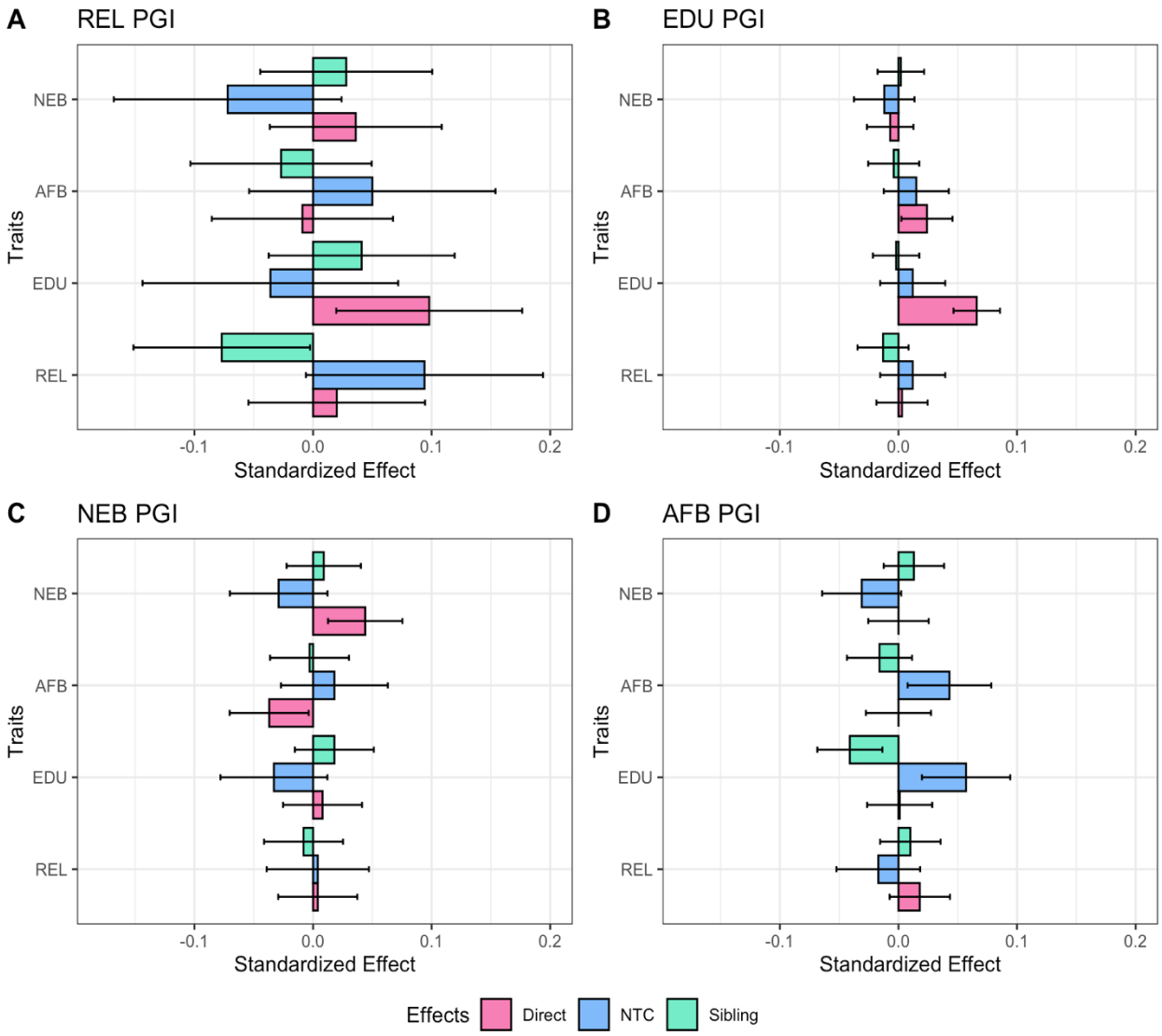
Table C.1 Genotypic and phenotypic correlations between siblings for four traits in the WLS for Figure 4.3.1

Type	Traits	Estimate	Lower CI	Upper CI	NA
Genotypic	REL	0.506	0.474	0.537	0
Phenotypic	REL	0.150	0.108	0.191	36
Genotypic	EDU	0.530	0.499	0.560	0
Phenotypic	EDU	0.331	0.293	0.369	33
Genotypic	NEB	0.560	0.530	0.588	0
Phenotypic	NEB	0.089	0.047	0.131	0
Genotypic	AFB PGI	0.514	0.482	0.544	0
Phenotypic	AFB	0.141	0.095	0.186	345
Sibling pairs = 2,134, the last NA column shows the number of missing pairs					

Table C.2 Decomposition of total PGI effects into direct effects and average nontransmitted coefficients (NTC) for Figure 4.3.2

Traits	PGI Predictor	Direct effects		NTC		Total Effects		N [unique individuals with nonmissing phenotypes]
		Coefficient	SE	Coefficient	SE	Coefficient	SE	
REL	REL	0.075	0.027	0.002	0.023	0.077	0.016	4212
EDU	REL	0.066	0.024	0.015	0.023	0.078	0.016	4215
NEB	REL	0.018	0.027	-0.039	0.023	-0.019	0.016	4238
AFB	REL	0.010	0.028	0.018	0.024	0.026	0.017	3881
REL	EDU	0.012	0.007	-0.003	0.006	0.009	0.004	4212
EDU	EDU	0.067	0.006	0.009	0.006	0.075	0.004	4215
NEB	EDU	-0.009	0.007	-0.010	0.006	-0.019	0.004	4238
AFB	EDU	0.027	0.008	0.010	0.006	0.037	0.004	3881
REL	NEB	0.009	0.012	-0.005	0.010	0.004	0.007	4212
EDU	NEB	-0.006	0.011	-0.011	0.010	-0.016	0.007	4215
NEB	NEB	0.038	0.012	-0.019	0.010	0.019	0.007	4238
AFB	NEB	-0.036	0.012	0.015	0.010	-0.021	0.007	3881
REL	AFB	0.011	0.009	-0.005	0.008	0.007	0.005	4212
EDU	AFB	0.033	0.008	0.006	0.008	0.038	0.005	4215
NEB	AFB	-0.008	0.009	-0.016	0.008	-0.024	0.005	4238
AFB	AFB	0.011	0.010	0.024	0.008	0.035	0.006	3881

Figure C.3 Decomposition of PGI effects into direct effects, average non-transmitted coefficients (NTC), and indirect sibling effects



D. Intrafaith vs Interfaith Marriage

Figure D.1 The proportion of interfaith marriange by birth cohorts among non-Hispanic white spousal pairs in the HRS, with genotyping data [all marriages]

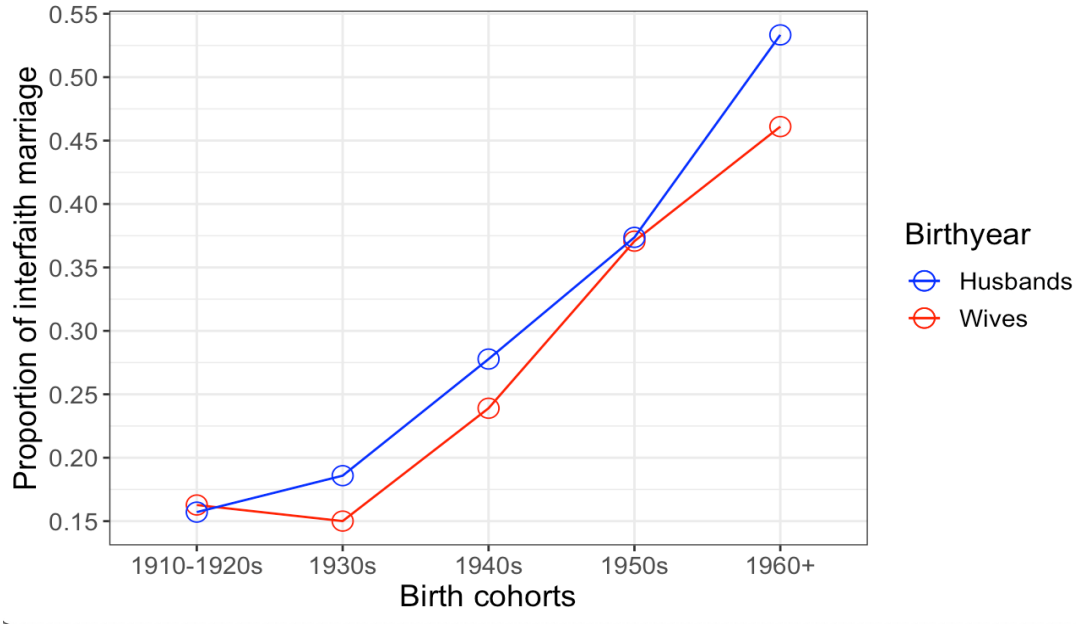
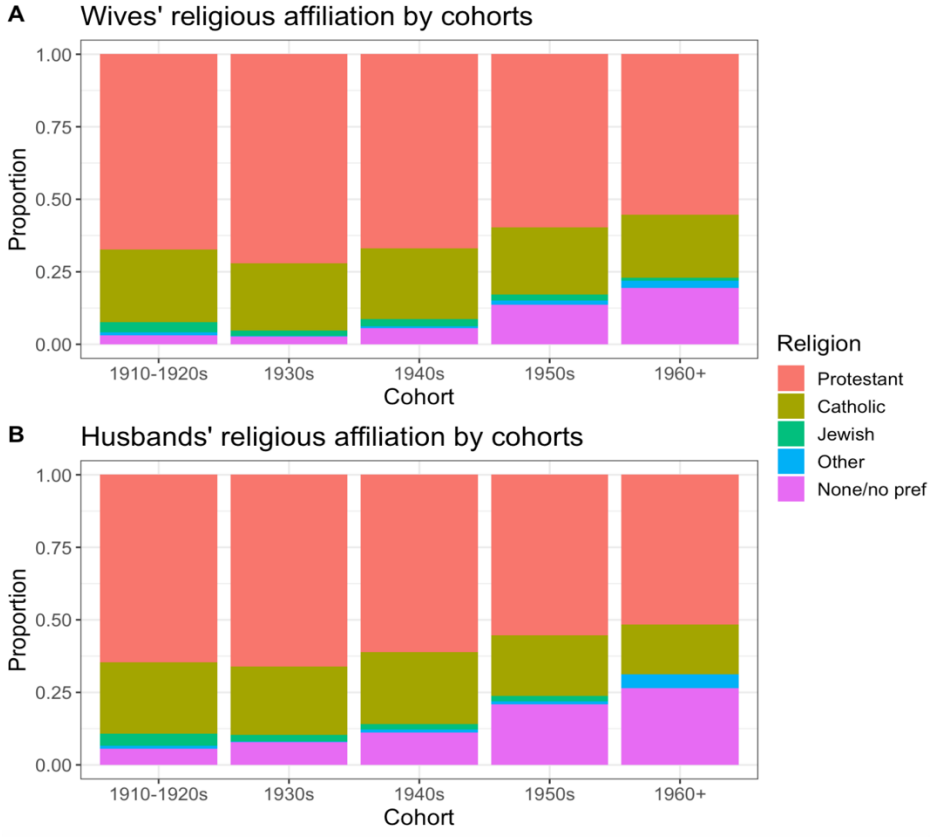


Figure D.2 The proportion of religious affiliation by birth cohorts and gender among non-Hispanic white spousal pairs in the HRS, with genotyping data [all marriages]



Chapter 3 Gene-environment interactions: adverse life events, religious attendance, and depressive symptoms

1. Introduction

The relationship between adverse life events and mental health has been widely studied, and many scholars have found that adverse life events appear to be a precipitating factor in the onset of depressive symptoms for people of all ages(Gerber et al., 2018; Kessler, 1997; Kraaij et al., 2002; Low et al., 2012). The relationship was found to vary considerably depending on many characteristics of the people experiencing the adverse life events (Fritz et al., 2018; Kessler, 1997; Taylor & Aspinwall, 1996). Access to social support has been repeatedly shown to predict an attenuation of this relationship (Dalgard et al., 1995; Kessler, 1997; Kornblith et al., 2001; Zhang, 2017). As religious service attendance could be considered one way of accessing social support and religious beliefs may provide positive coping strategies as a stress buffer, the evidence generally demonstrates that religious attendance moderates adverse life events and depression (Abernethy et al., 2002; Ahles et al., 2016; Bjorck & Thurman, 2007; Carpenter et al., 2012; Park et al., 1990; Schnittker, 2001; Sherkat & Reed, 1992; Young et al., 2000). However, most of the previous studies in psychiatry did not use a nationally representative sample, potentially limiting the generalizability of their findings.

Further, it is essential to recognize that numerous unmeasured confounding variables could influence the observed associations between religious attendance and depressive symptoms. For instance, genetic sensitivity might play a critical role in this relationship. Certain genetic variations in individuals may make them more or less responsive to the potential mental health benefits associated with religious attendance. Given the complexity of factors at play, it becomes increasingly difficult to ascertain the validity of the "stress moderators" identified in these studies without employing a causal design. Consequently, the conclusions drawn from such research should be treated with caution, as they may not accurately capture the true nature of the connection between religious attendance and depression. By acknowledging the methodological limitations of previous studies, we can incorporate genetic data and use a quasi-experiment design to have a better understanding of the moderating effect of religious attendance and explore gene-environment interaction on depressive symptoms among Americans. This chapter uses regression discontinuity design and two nationally representative samples, the Health and Retirement Study (HRS) and The National Longitudinal Study of Adolescent to Adult Health (Add Health) to answer the following research questions.

Research questions:

1. **Among younger US adolescents and adults, did religious attendance increase after the 9/11 terrorist attacks, and did more religious individuals have fewer depressive symptoms?**
2. **Among older US adults, did more religious individuals have fewer depressive symptoms after the death of a spouse? Can religious attendance help ease the grief of losing a spouse?**

2. Literature Review

Influential papers (Cassel, 1976; Cobb, 1976) since the 1970s suggested that social support may protect against the health consequences of life stress. Henderson (1992) reviewed 35 studies assessing the relationship between social support and depression and found that 31 studies reported such a buffering or protective effect. Similar findings were reported for the buffering effect of religiosity on the negative impact of adverse life events on mental health (Bjorck & Thurman, 2007; Kuhn & Brulé, 2019; Lorenz et al., 2019; Strawbridge et al., 1998). While some studies support the buffering effect hypothesis, other evidence supports the main/direct effect or additive model hypothesis, in which social support directly influences mental health irrespective of the presence of adverse life events (Cohen & Syme, 1985; Kornblith et al., 2001; Turner, 1981; Turner & Noh, 1983). Religiosity's moderating

effect is more complicated: some studies have found that religiosity could exacerbate some life stressors, such as marital problems and abuse (Strawbridge et al., 1998), and religious salience, as measured by the self-reported importance of religion, rather than religious attendance, has been found to act as a buffering effect against the negative impact of stressful life events (Schnittker, 2001). In general, a higher level of religiosity, primarily measured by religious attendance was found to be associated with fewer depressive symptoms (Braam & Koenig, 2019; Miller et al., 2012; Oman & Thoresen, 2002; Smith et al., 2003). Figures 2.1 and 2.2 respectively depict the direct effect and buffering effect hypotheses of religiosity on mental health. However, it is also possible that religiosity has both direct and buffering effects on mental health, as illustrated in Figure 2.3.

Gene-environment interactions (GxE) have been offered as an explanation of differential responses to adverse life events. The landmark studies discovered a functional polymorphism in the 5-HTT gene that was shown to moderate the influence of stressful life events on depression (Caspi et al., 2003), and a functional polymorphism in the promoter region of the monoamine oxidase A (MAOA) gene was shown to moderate the impact of childhood maltreatment on the risk of developing antisocial behavior (Caspi et al., 2002). Recent replications and meta-analyses have generally supported the original findings concerning gene-environment interactions in mental health, but disputes and inconsistencies remain,

highlighting the need for further investigation with a more rigorous research design. (Byrd & Manuck, 2014; Caspi et al., 2010; Karg et al., 2011; Kim-Cohen et al., 2006; Uher & McGuffin, 2010). Fletcher (2014) utilized Add Health data and regression discontinuity to investigate the main effect of the September 11 terrorist attacks on reports of feelings of sadness, by examining three additional genes (DRD2, DRD4, and DAT1). The study did not find an interaction with 5-HTT, but confirmed the interaction effect of MAOA in men and presented new evidence for the DRD4 gene. As GxE research in mental health is shifting from a candidate gene to a genome-wide approach (Assary et al., 2018), the polygenic index (PGI, i.e., polygenic score) was used to investigate genetic heterogeneity in depressive symptoms following the death of a spouse using HRS data (Domingue et al., 2014). They reported that individuals with a higher well-being PGI were able to mitigate the impact of increased depressive symptoms following the death of a spouse.

Further, the investigation of HRS data using logistic and negative binomial regression supported the finding that a depression PGI moderated the relationship between stressful life events and depression (Musliner et al., 2015). Without considering the effect of religiosity, GxE research on the moderators of adverse life events' impact on mental health so far may be ignoring a crucial individual characteristic for Americans and a potentially effective coping strategy for people experiencing negative life events. A previous study on religious responses

to the 9/11 terrorist attacks suggested that young American adults exhibited a short-lived and modest increase in religious salience and prayer, and those with a top ten percent CESD score and little to no religious commitment were most likely to turn to religion after 9/11 to compensate for their lack of social and psychological support (Uecker, 2008).

We used a quasi-experimental design and a gene-environmental interaction framework to test whether religious attendance has a direct or a buffering effect or both on depressive symptoms following a stressful life event. We re-examined the evidence of differential responses to the 9/11 attacks among American adolescents and adults using Add Health data and differential responses to spousal death among elderly Americans using HRS data. By incorporating the religious attendance PGI from Chapter 1 and religious attendance for each relevant wave of the survey, we can also examine the religious responses to adverse life events controlling for genetic predisposition to religious attendance.

Adverse life events, such as receiving news of the 9/11 attacks and experiencing a spousal death, can significantly impact an individual's psychological well-being (Bonanno et al., 2006; Stroebe et al., 2007). While both events are undoubtedly distressing, they possess some key similarities and differences in terms of their effects on individuals. Similarities between these events include the emotional distress they cause, as both receiving news of the 9/11

attacks and experiencing a spousal death can lead to feelings of sadness, anxiety, fear, and anger (Bonanno et al., 2006; Stroebe et al., 2007). Moreover, these events can trigger or exacerbate mental health issues, such as depression, anxiety disorders, or post-traumatic stress disorder (PTSD) (Neria et al., 2008; Zisook & Shear, 2009). Individuals affected by either of these events might turn to various coping mechanisms, including social support, therapy, and religion or spirituality, in an attempt to deal with their emotional pain and adapt to their new circumstances (Pargament et al., 2011; Stroebe et al., 2007).

Differences between these events primarily lie in the nature of the trauma experienced. Experiencing a spousal death is a deeply personal and individual loss (Stroebe et al., 2007), while receiving news of the 9/11 attacks represents a collective trauma shared by a larger community or even an entire nation (Neria et al., 2008). The grieving process associated with spousal death involves feelings of loneliness, guilt, and a need to restructure one's life (Zisook & Shear, 2009), whereas the 9/11 attacks evoked a sense of collective grief, with many people feeling shocked, fearful, and insecure about the future (Bonanno et al., 2006). The duration and intensity of the impact also differ between these events. The psychological impact of a spousal death might be more enduring and intense, as it directly affects the individual's day-to-day life and future plans (Stroebe et al., 2007). In contrast, the 9/11 attacks, while undoubtedly traumatic, may not have the same long-lasting and intense impact

on an individual's life, as it is a more distal event (Neria et al., 2008). It's worth noting that widowhood may not be entirely exogenous, as shared living conditions and health-related risk factors before spousal death could be confounding factors. In contrast, the 9/11 attacks were an exogenous shock, as they were sudden and unpredictable. Lastly, the social support and response elicited by these events differ. In the case of a spousal death, friends, family, and community members often rally around the bereaved individual, providing emotional and practical support (Stroebe et al., 2007). The 9/11 attacks, on the other hand, elicited a broader societal response, including increased security measures, changes in international relations, and the initiation of military interventions (Neria et al., 2008).

In conclusion, both the 9/11 attacks and spousal death are adverse life events causing significant emotional and psychological distress, yet they differ in their personal or collective nature, grieving process, impact duration and intensity, and the social support and response they elicit. Analyzing gene-environment interactions in relation to these events can further highlight their similarities and unique aspects.

Figure 2.1 - Direct effect hypothesis

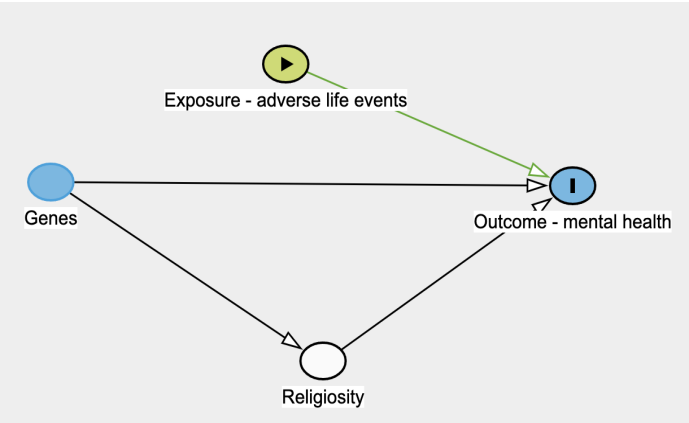


Figure 2.2 - Buffering effect hypothesis

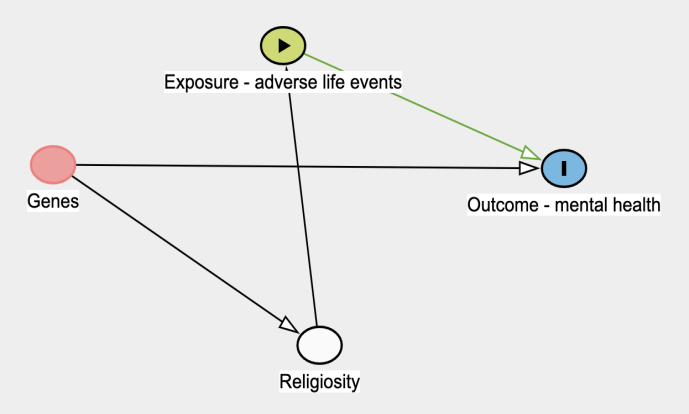
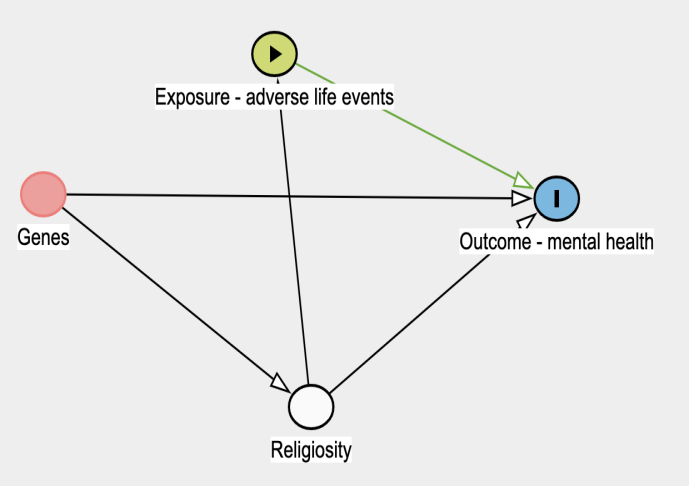


Figure 2.3 - Mixed effect hypothesis



3. Data and Methods

Wave 3 [2001-2002] of the National Longitudinal Study of Adolescent Health (Add Health) covered the months before and after the 9/11 terrorist attacks in 2001 and had measurement of religious attendance and nine items of the Center for Epidemiologic Studies Depression (CESD) Scale as a measure of depressive symptoms (Harris, Kathleen Mullan, 2018; Roberts et al., 1991). Previous evidence has focused on one question about how often the respondent "was sad during the past seven days" and compared the differential responses before and after the date of 9/11/2001 to evaluate a short-lived effect of increased depressive symptoms (Fletcher, 2014; Ford et al., 2003). Sadness is only one of the nine CESD items[8]. Instead of focusing on sadness, we used nine CESD items adapted from the original 20-item CESD scale[9] (Radloff, 1977), which has been widely used in measuring depressive symptoms (Blazer et al., 1987; Steffens et al., 2009). It is important to note that Add Health only includes nine out of the 20 standardized CESD items, which may limit the validity of our findings compared to studies using the full CESD scale. The largest possible score is 27, and the maximum observed value, as shown in Table 3.1 is 24.

[8] The nine items are listed here in response to "How often was the following true during the past seven days?"1. You were bothered by things that usually don't bother you. 2. You could not shake off the blues, even with help from your family and your friends. 3. You felt you were just as good as other people. [positive]. 4. You had trouble keeping your mind on what you were doing. 5. You were depressed. 6. You were too tired to do things. 7. You enjoyed life. [positive] 8. You were sad. 9. You felt that people disliked you.

[9] Zero for "Rarely or none of the time (less than 1 day)"; One for "Some or a little of the time (1-2 days)"; Two for "Occasionally or a moderate amount of time (3-4 days)"; Three for "Most or all of the time (5-7 days)". The scoring of positive items is reversed.

With genome-wide association study (GWAS) data available, we were able to create polygenic indices (PGIs) for both religious attendance and depression among non-Hispanic whites. The details of religious attendance PGI construction are available in Chapter 1, and the PGI with the best prediction was chosen for this chapter[10]. We used the same method[11] to calculate a depression PGI based on the Social Science Genetic Association Consortium GWAS on depressive symptoms (Okbay et al., 2016). The two PGIs are negatively correlated for wave 3 respondents with a correlation coefficient of -0.06 and a 95% confidence interval of [-0.085, -0.029].

We restricted the key analysis to a 60-day window around 9/11, i.e., from the 30 days before 9/11 to the 30 days after 9/11, because the main effect reported in previous studies was very short-lived (Fletcher, 2014; Uecker, 2008). In addition, we conducted sensitivity analyses on a 120-day window and the entire time of Wave 3 from April 2001 to May 2002 (Harris, 2013) in Supplementary Table A.9.a. Table 3.1 below presents descriptive statistics of the subsample within the 60-day window, and Table A.1 in the Supplementary Materials presents the descriptive analysis of a larger sample of non-Hispanic whites not limited by time in Wave 3. The subsample is very similar to the larger sample in terms of key statistics.

[10] We used the PGI from binary coding [more than half] strategy and the interaction of birth year and sex and top 10 principal components as covariates.

[11] We used the mean score of CESD scales [a continuous variable] across four waves as the phenotype and same covariates used for constructing religious attendance PGI to construct depression PGI.

Table 3.1 Add Health descriptive statistics, non-Hispanic whites interviewed surrounding the 60-day window [N = 1,710] of September 11, 2001, with genotypic data

Variable	Mean	SD	Range
Gender -Female	0.55	Binary	[0, 1]
Age	21.55	1.69	[18, 26]
Years of education	13.22	1.91	[6, 22]
Region - Northeast	0.14	Binary	[0, 1]
Region - South	0.33	Binary	[0, 1]
Region - West	0.21	Binary	[0, 1]
After 9/11 indicator	0.46	Binary	[0, 1]
Interview date centered around 9/11	-0.70	17.26	[-30, 30]
CESD scale [9-item]	4.48	3.97	[0, 24]
Sadness	0.56	0.70	[0, 3]
Depression PGI	-0.03	0.98	[-4.31, 2.73]
Religious attendance [times/year]	15.88	25.18	[0, 90]
Religious attendance [>= weekly]	0.16	Binary	[0, 1]
Religious attendance PGI	0.04	1.02	[-3.46, 3.45]

Within the quasi-experimental and sharp[12] regression discontinuity design (RDD) framework, we used linear models to predict depressive symptoms as measured by CESD scores and

[12]In a sharp RDD, the cutoff is sharp or deterministic, meaning that a small change in the score on the discontinuity variable leads to a sharp change in the probability of receiving the treatment (Dunning, 2012). In contrast, in a fuzzy RDD, the cutoff is fuzzy or probabilistic, meaning that a small change in the score on the discontinuity variable leads to a gradual change in the probability of receiving the treatment. The probability of treatment, which is the exogenous shock of 9/11, changed from 0 to 1 right after knowing the break news of the terrorist attacks.

incorporated a function for the running variable (i.e., interview time as the distance from 9/11), since a previous study pointed out the possible seasonality of depression (Ford et al., 2003). This is the general form of the linear model to detect GxE effects:

$$\textit{Depressive symptoms} = \alpha + \beta_1 PGI + \beta_2 Post9/11 + \beta_3 PGI \times Post9/11 + \beta_4 X + \beta_5 f(interview\ time) + \varepsilon,$$

where PGI is a polygenic index that measures an individual's genetic predisposition for religious attendance or depressive symptoms using genome-wide data. More detailed information about the construction of the PGI can be found in Chapter 1. Post9/11 is a binary indicator variable reflecting whether the interview is before or after the terrorist attacks on 9/11; X is a vector of demographic characteristics, including age, gender, years of education, and region of residence; $f(interview\ time)$ is a flexible function of the specific interview date measured as days from 9/11/2001; α is the model intercept, ε is a random error term with a normal distribution and β_3 is the coefficient measuring the interaction between a genotype and the exogenous environmental exposure.

The key assumption of RDD is that the respondents interviewed before and after 9/11 were highly similar in both observed and unobserved predictors of depressive symptoms. In order to assess the direct effect of religious attendance on depressive symptoms while controlling for individual genotypes, it is also necessary to examine whether religious attendance exhibited comparable levels around the cut-off point, as this would influence the predictors

for depressive symptoms. Since the previous study suggested differential religious responses to 9/11 (Uecker, 2008), we used similar linear models to detect GxE effects on religious attendance as follows:

$$\textit{Religious attendance} = \alpha + \beta_1 PGI + \beta_2 Post9/11 + \beta_3 PGI \times Post9/11 + \beta_4 X + \beta_5 f(interview\ time) + \varepsilon$$

The assumption could be compromised if GxE interactions are found for religious attendance, and religious attendance varied around the time of 9/11. GxE interactions might also imply that religious attendance has a buffering effect on depression. However, the current research design and available data do not allow for a clear disentanglement of the reverse causal pathway between depression and religious attendance.

HRS is a longitudinal study that surveys a representative sample of more than 20,000 Americans over age 50 every two years (The University of Michigan, 2020). Compared to Add Health respondents, the HRS subsample in this chapter was much older, with a larger proportion of women, as we restricted the samples to those who have experienced the death of their spouse. From the first wave in 1992 to the fourteenth wave in 2018, 2,600+ individuals experienced a spousal death. These survivors completed at least one follow-up survey after their spouse's death. It is important to note that the HRS collected only eight out of the 20 standardized CESD items to measure depressive symptoms[13] for each wave from

[13] The eight questions have binary answers - Yes or No. The 8-item CESD score summarized eight binary answers ranging from 0 to 8. The scoring of positive items is reversed. "Now, think about the past week and the feelings you have experienced. Please tell me if each of the following was true for you much of the time during the past week." 1.You felt

1992 to 2018, and religious attendance was not collected in 1998 and 2002 (Eaton et al., 2004; The University of Michigan, 2020).

We used the religious attendance PGI with the best prediction from Chapter 1[14] and the depression PGI constructed from the same GWAS summary statistics as aforementioned on depressive symptoms among non-Hispanic whites[15] (Okbay et al., 2016). Table 3.2 displays descriptive statistics for the final subsample of 2,437 respondents, representing 7,911 observations within a 120-month window that includes the 60 months before and after spousal death. Sensitivity analysis in Supplementary Figure B.2 also replicated previous findings using a subjective well-being PGI from the same GWAS study of depressive symptoms (Okbay et al., 2016). The correlation between the religious attendance PGI and the depression PGI is not statistically significant, while the depression PGI and the well-being PGI are negatively associated with a correlation coefficient of -0.30 and a 95% confidence interval of [-0.33, -0.26]. The standardization of PGIs for the non-Hispanic whites with genetic data ensures that the mean is set to 0 and the standard deviation to 1. The descriptive statistics in Tables 3.1 and 3.2 show that the distribution of PGIs around adverse life events

depressed. 2. You felt that everything you did was an effort. 3. Your sleep was restless. 4. You were happy [positive]. 5. You felt lonely. 6. You enjoyed life [positive]. 7. You felt sad. 8. You could not "get going."

[14] We used the PGI from binary coding [more than half] strategy, and the covariates include the first and second-degree polynomial of the interaction of birth year and sex and top 10 principal components.

[15] We used the mean score of CESD scales [a continuous variable] across fourteen waves as the phenotype and the same covariates used for constructing religious attendance PGI to construct depression PGI.

closely aligns with this standardized distribution. This is evident from the mean value being close to zero and the standard deviation being close to one.

Table 3.2 HRS descriptive statistics, non-Hispanic whites interviewed surrounding the 120-month window [N = 2,437, obs = 7,911] of spousal death, with genotypic data and phenotypic data reporting depressive symptoms and religious attendance in the same wave of the survey.

Variable	Mean	SD	Range
Gender -Female	0.73	Binary	[0, 1]
Age [Post-spousal death]	72.34	9.98	[35.68, 96.22]
Years of education	12.75	2.46	[0, 17]
Post-spousal death indicator	0.53	Binary	[0, 1]
Interview date centered around spousal death (Unit: Months)	0.73	33.12	[-59.90, 59.85]
CESD scale [8-item] (individual-level[16])	1.44	1.31	[0, 8]
CESD scale [8-item] (obs-level[17])	1.66	2.05	[0, 8]
Depression PGI	0.01	1.00	[-3.05, 3.12]
Subjective wellbeing PGI	-0.01	0.99	[-3.44, 3.25]
Religious attendance [times/year] (individual-level)	35.78	29.04	[0, 116.88]
Religious attendance [times/year] (obs-level)	35.85	33.94	[0, 150]

[16] Summarized by the mean scale of available data across the waves for each respondent

[17] Weighted by the inverse of the number of observations per respondent

Religious attendance [>= weekly] (individual-level)	0.29	Binary	[0, 1]
Religious attendance [>= weekly] (obs-level)	0.45	Binary	[0, 1]
Religious attendance PGI	0.00	0.99	[-4.45, 3.49]

To understand changes in depressive symptoms and religious attendance from before to after the adverse events [i.e., 9/11 attacks and spousal deaths], we used nonparametric and parametric local regression to analyze subsets of data on each side of the event (Lindstrom & Bates, 1990; McCrary, 2008). While spousal death may not be completely exogenous, its timing is often unpredictable, and we applied the same methods to analyze changes surrounding this event. If the trajectories demonstrate a jump after the adverse event, the discontinuity of the regression lines is most likely to be caused by the adverse event. We used similar figures to describe trajectories of depression and religious attendance across various groups of respondents before and after the 9/11 attacks and spousal deaths among Add Health and HRS participants, respectively, categorized by different levels of PGI. To quantify the GxE effects, we used similar linear models to predict depression and religious attendance for HRS respondents:

$$\textit{Depressive symptoms} = \alpha + \beta_1 PGI + \beta_2 PostSD + \beta_3 PGI \times PostSD + \beta_4 X + \beta_5 f(interview\ time) + \varepsilon ,$$

$$\textit{Religious attendance} = \alpha + \beta_1 PGI + \beta_2 PostSD + \beta_3 PGI \times PostSD + \beta_4 X + \beta_5 f(interview\ time) + \varepsilon ,$$

where PostSD is a binary indicator variable reflecting whether the interview is before or after the spousal death; X is a vector of demographic characteristics, including age, gender, and years of education. The coefficient of interest is β_3 , reflecting GxE effects. Each HRS respondent may have multiple waves of observations either before or after the spousal deaths. Thus, the linear regression is weighted by the inverse of the number of observations per individual to adjust the sample size of different respondents within our dataset.

The previous study (Domingue et al., 2017) illustrated non-linear trajectories of depression after spousal death, characterized by a rapid decline in the immediate aftermath of the loss, followed by a slower decline in the subsequent period. We also replicated previous findings using nonlinear least square models as follows:

$$\textit{Depressive symptoms} = \alpha + \beta_1 PGI + (\beta_2 + \beta_3 PGI) exp[-t/(\lambda + \gamma PGI)] + \beta_4 X + \varepsilon ,$$

where t is the interview time since the death, and $(\lambda + \gamma PGI)$ estimates the decay/attenuation rate of the depressive symptoms over time with a population average decay rate λ and PGI-dependent decay rate γ. β_1 estimates the direct effect of PGI on depressive symptoms regardless of spousal death, while β_2 estimates the main effect of spousal death and β_3 estimates the interaction between PGI and the entire decay function right after spousal death. Both γ and β_3 can help test the genetic heterogeneity of the decay rate over time and the genetic heterogeneity of depressive symptoms right after the loss of the spouse. X

covariates include age, gender, and years of education. We restricted samples to the first observations after spousal death for non-linear modeling.

We conducted all statistical analyses using R software. To fit smooth lines of local non-parametric models, we used the loess [LOESS] function, and for linear regression, we used the lm_robust function from the "estimatr" package. We used the nlsLM function from the "minpack.lm" package to fit Nonlinear Least Squares (NLS) models.

4. Results

1. Responses to 9/11: Evidence from the Add Health study

The only significant GxE effect detected by both Figure 4.1.1 and Table 4.1.2 is the interaction between religious attendance PGI and the exposure of 9/11 in predicting religious attendance. Higher religious attendance PGI predicts more frequent religious attendance and the increase in religious attendance is even greater after 9/11 among those with a higher religious attendance PGI. In other words, those with a higher genetic predisposition for being more religious may respond more substantially after being exposed to tragic news such as the 9/11 terrorist attacks by attending more religious activities right after the stressful event. However, as both Figure 4.1.1 below and Supplementary Figure A.5.b illustrate, this change of behavior only lasted for around 20 days after 9/11 compared with almost zero religious

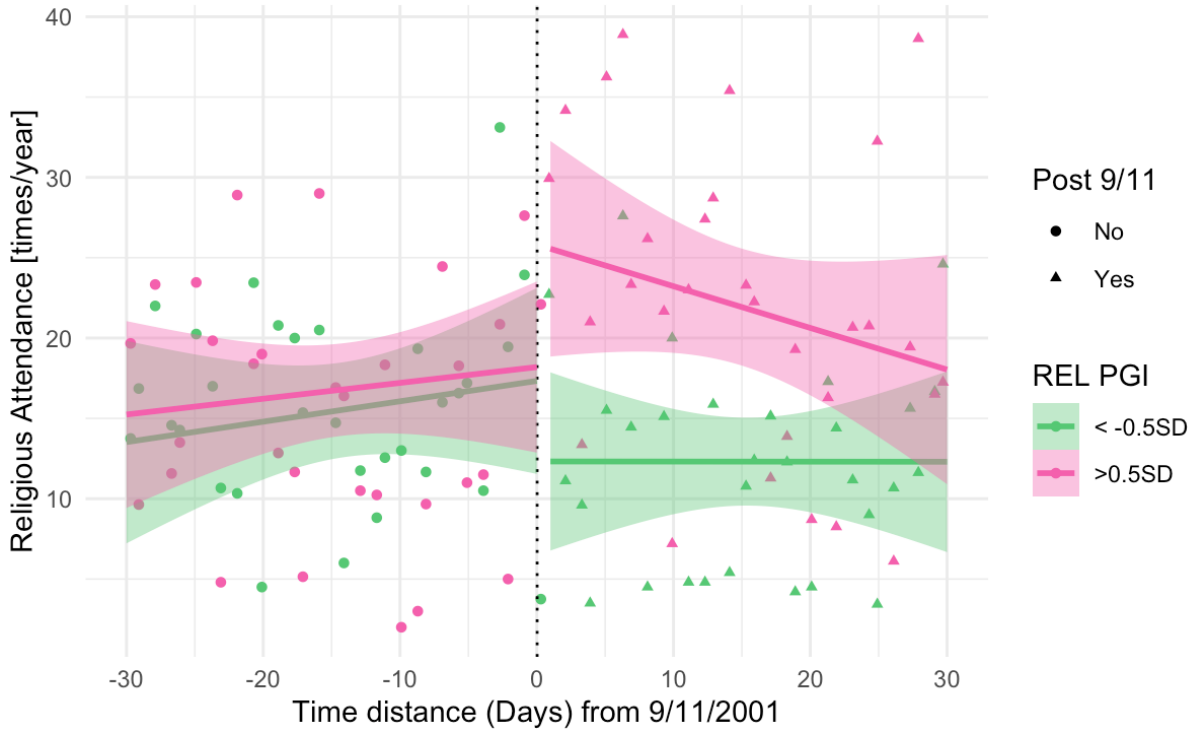
response among the respondents with a low religious attendance PGI. Supplementary Figure A.5.c shows that there is no significant difference when religious attendance is residualized on the religious attendance PGI.

Model 4 and Model 5 in Table 4.1.3 use religious attendance to predict the CESD scores and demonstrate a negative association between more frequent religious attendance and depressive symptoms with statistical significance after controlling for both the religious attendance PGI and the depression PGI. Therefore, the key RDD assumption in the previous study (Fletcher, 2014) is violated since r religious attendance as an observed predictor of depressive symptoms "jumped" after exposure to adverse events among respondents with a high religious attendance PGI. The results from both Table 4.1.2 and Table 4.1.3 suggest religious attendance may have both direct and buffering effects on depressive symptoms, which supports the hypothesis of mixed effects. Both genetic factors and environmental exposure to adverse events would be confounding variables for depression and religious attendance.

The trajectories of depressive symptoms from Figures A.2 to A.4 in the Supplementary Materials show a slightly elevated CESD score right after 9/11 that dropped back to the pre-9/11 level within a month. The increase is especially salient for predicting sadness shown in Table A.8.b. Gender, education, and the region of residence are additional confounders for

predicting both religious attendance and depression. More years of education and living in the South are positively associated with more religious attendance, while being a male and living in the Northeast are negatively associated with religious attendance. Being a male and having more years of education are negatively associated with higher CESD scores, while living in the Northeast, where 9/11 happened, is positively associated with more depressive symptoms. After controlling for these confounders, religious attendance and depression are still weakly associated among Add Health respondents. The GxE effect of candidate genes [e.g., MAOA] on depressive symptoms after 9/11 was not reproduced by using PGI in this chapter.

Figure 4.1.1 Trajectories of religious attendance for Add Health respondents with a high religious attendance (REL) PGI and a low REL PGI within a 60-day window of the 9/11 attack[18]



[18] Trajectories for respondents with a high religious attendance PGI are graphed in red (more than 0.5 standard deviations above the mean, N = 564 [60 days]), while those with low PGI are graphed in green (more than 0.5 standard deviations below the mean, N=519 [60 days])

Table 4.1.2 Linear models predicting religious attendance [times/year] among non-Hispanic whites interviewed surrounding the 60-day window [N = 1,710] of September 11, 2001, with genotypic data[19]

	REL(60) Model1	Model2	Model3	Model4	Model5
(Intercept)	−6.320	−6.877	−6.437	−3.403	−3.650
	(8.156)	(8.180)	(8.150)	(8.218)	(8.263)
GenderMale	−3.680**	−3.522**	−3.652**	−4.156***	−4.149***
	(1.199)	(1.208)	(1.200)	(1.209)	(1.209)
Age	0.024	−0.044	0.027	0.042	0.041
	(0.370)	(0.372)	(0.369)	(0.369)	(0.369)
Edyears	1.507***	1.657***	1.509***	1.411***	1.416***
	(0.313)	(0.315)	(0.314)	(0.313)	(0.314)
RegionNortheast	−5.094**	−4.926**	−5.072**	−5.013**	−5.026**
	(1.578)	(1.554)	(1.576)	(1.574)	(1.574)
RegionSouth	7.968***	7.828***	7.913***	7.840***	7.842***
	(1.507)	(1.520)	(1.505)	(1.502)	(1.502)
RegionWest	1.765	1.903	1.779	1.831	1.819
	(1.661)	(1.677)	(1.662)	(1.661)	(1.665)
Post911	2.208	2.557	2.236	2.632	3.086
	(2.372)	(2.415)	(2.365)	(2.368)	(2.814)
Time	−0.057	−0.062	−0.062	−0.055	−0.056
	(0.097)	(0.097)	(0.097)	(0.097)	(0.097)
REL_PGI	1.057		1.117	1.057	1.065
	(0.844)		(0.845)	(0.837)	(0.836)
Post911 × Time	−0.006	−0.017	−0.001	−0.022	−0.024
	(0.141)	(0.142)	(0.140)	(0.140)	(0.140)
Post911 × REL_PGI	3.269**		3.176**	3.192**	3.176**
	(1.218)		(1.220)	(1.211)	(1.209)
DEP_PGI		0.915	0.974	1.011	1.006
		(0.883)	(0.889)	(0.883)	(0.884)
Post911 × DEP_PGI		−1.682	−1.472	−1.424	−1.408
		(1.234)	(1.221)	(1.216)	(1.218)
CESD9				−0.414**	−0.370+
				(0.146)	(0.201)
Post911 × CESD9					−0.092
					(0.290)
Num.Obs.	1710	1710	1710	1710	1710
R2	0.064	0.050	0.065	0.069	0.069
R2 Adj.	0.058	0.044	0.058	0.062	0.061
AIC	15 797.4	15 822.6	15 799.7	15 794.2	15 796.1
BIC	15 868.2	15 893.3	15 881.3	15 881.3	15 888.7
RMSE	24.35	24.53	24.34	24.29	24.29

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

[19]Tables 4.1.2, 4.1.3, 4.2.2, and 4.2.6 present results from linear regression. Non-linear regression results are presented in Table B.8 and Tabl B.9 in Supplementary Materials.

Table 4.1.3 Linear models predicting depressive symptoms (9-item CESD score) among non-Hispanic whites interviewed within the 60-day window [N = 1,710] of September 11, 2001, with genotypic data

	CESD [9-item] Model1	Model2	Model3	Model4	Model5
(Intercept)	7.341***	7.416***	7.323***	7.256***	7.252***
	(1.304)	(1.301)	(1.303)	(1.299)	(1.300)
GenderMale	−1.225***	−1.216***	−1.216***	−1.254***	−1.255***
	(0.190)	(0.190)	(0.190)	(0.190)	(0.190)
Age	0.041	0.035	0.036	0.037	0.036
	(0.058)	(0.058)	(0.058)	(0.058)	(0.058)
Edyears	−0.245***	−0.241***	−0.237***	−0.221***	−0.221***
	(0.053)	(0.053)	(0.053)	(0.054)	(0.054)
RegionNortheast	0.144	0.170	0.142	0.089	0.088
	(0.294)	(0.295)	(0.294)	(0.295)	(0.296)
RegionSouth	−0.169	−0.171	−0.175	−0.092	−0.093
	(0.233)	(0.232)	(0.232)	(0.231)	(0.231)
RegionWest	0.127	0.122	0.126	0.144	0.144
	(0.274)	(0.274)	(0.274)	(0.274)	(0.274)
Post911	0.953*	0.950*	0.954*	0.978**	1.012*
	(0.377)	(0.378)	(0.378)	(0.378)	(0.393)
Time	0.016	0.016	0.016	0.015	0.016
	(0.014)	(0.014)	(0.014)	(0.014)	(0.014)
DEP_PGI	0.097		0.088	0.099	0.098
	(0.134)		(0.135)	(0.134)	(0.134)
Post911 × Time	−0.050*	−0.051*	−0.051*	−0.051*	−0.051*
	(0.022)	(0.022)	(0.022)	(0.022)	(0.022)
Post911 × DEP_PGI	0.114		0.117	0.101	0.101
	(0.192)		(0.194)	(0.193)	(0.194)
REL_PGI		−0.150	−0.145	−0.134	−0.135
		(0.118)	(0.119)	(0.119)	(0.119)
Post911 × REL_PGI		0.031	0.039	0.072	0.078
		(0.177)	(0.178)	(0.176)	(0.179)
attend_REL				−0.010**	−0.010*
				(0.004)	(0.005)
Post911 × attend_REL					−0.002
					(0.007)
Num.Obs.	1710	1710	1710	1710	1710
R2	0.047	0.046	0.048	0.052	0.052
R2 Adj.	0.040	0.040	0.040	0.044	0.043
AIC	9513.1	9513.8	9515.2	9509.8	9511.7
BIC	9583.9	9584.6	9596.9	9596.9	9604.2
RMSE	3.88	3.88	3.87	3.87	3.87

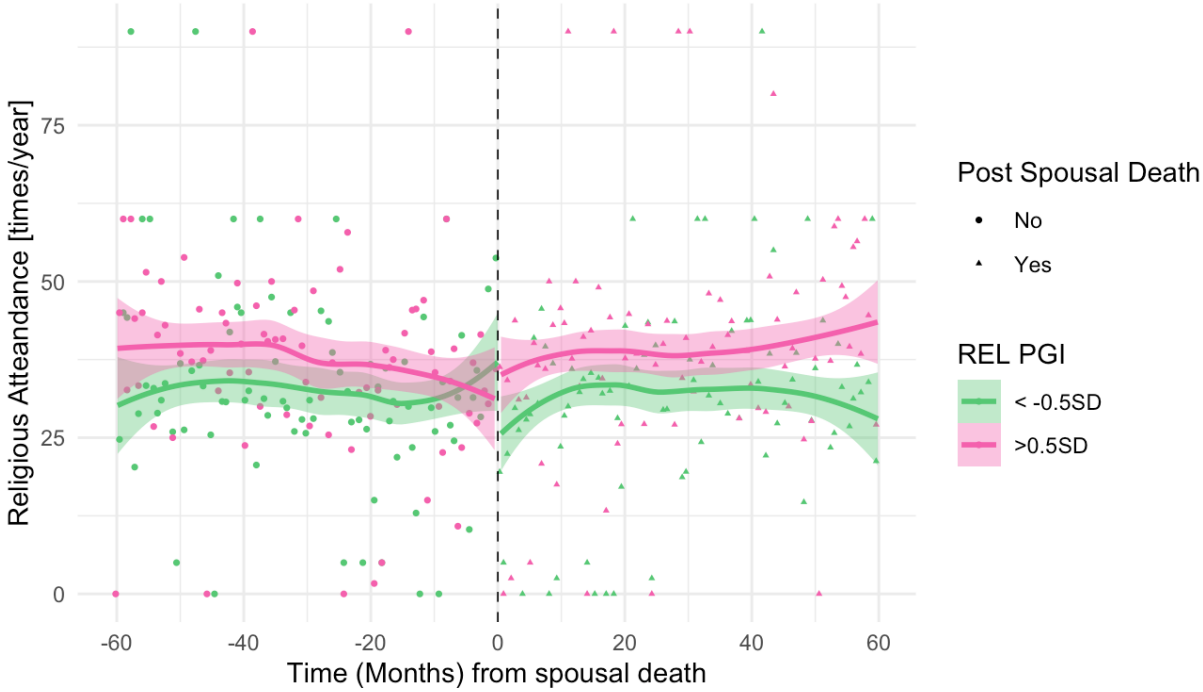
+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

2. Responses to spousal death: Evidence from the HRS study

As the trajectories of religious attendance for HRS respondents demonstrate in Figure 4.2.1, there is little change after spousal death, and a higher religious attendance PGI predicts more frequent religious attendance consistently over time. However, after controlling for the CESD

score and its interaction with the PostSD indicator in Model 5 of Table 4.2.2, we observe a large positive coefficient (5.2) of the PostSD indicator with statistical significance, indicating that spousal death is likely to increase religious attendance.

Figure 4.2.1 Trajectories of religious attendance for HRS respondents with a high religious attendance (REL) PGI and a low REL PGI - (local polynomial regression) [20]



There is no similar GxE effect of the religious attendance PGI and the exposure of adverse events among HRS respondents, in contrast to the discovery among Add Health respondents. Instead, the curves fitting trajectories of high and low religious attendance PGI predicting religious attendance are almost parallel before and after the spousal death. Similar trajectories can be observed in Supplemental Figures B.6 and B.7. Both depression PGI and depressive

[20] Trajectories for respondents with a high religious attendance PGI are graphed in red (more than 0.5 standard deviations above the mean, N=749, obs = 2,533), while those with a low PGI are graphed in green (more than 0.5 standard deviations below the mean, N=751, obs = 2,501).

symptoms negatively predict religious attendance with statistical significance. Table 4.2.2 also shows that older females attend religious activities more frequently.

Table 4.2.2 Linear models predicting religious attendance [times/year] among non-Hispanic white HRS respondents interviewed within the 120-month window [N = 2,437, obs = 7,911] of spousal death, with genotypic data

	Religiosity Model1	Model2	Model3	Model4	Model5
(Intercept)	−5.256	−6.513	−4.511	3.419	2.672
	(4.201)	(4.202)	(4.203)	(4.258)	(4.260)
GenderMale	−10.650***	−10.814***	−10.709***	−11.037***	−10.970***
	(0.982)	(0.984)	(0.981)	(0.975)	(0.976)
Age	0.468***	0.471***	0.462***	0.443***	0.442***
	(0.044)	(0.044)	(0.044)	(0.044)	(0.044)
Edyears	0.507**	0.582***	0.480**	0.264	0.271
	(0.177)	(0.176)	(0.177)	(0.177)	(0.177)
PostSD	1.517	1.583	1.627	3.772*	5.192**
	(1.679)	(1.681)	(1.678)	(1.698)	(1.891)
Time	−0.111**	−0.113**	−0.112**	−0.087*	−0.091*
	(0.039)	(0.039)	(0.039)	(0.039)	(0.038)
REL_PGI	2.227***		2.170***	2.008**	2.048***
	(0.623)		(0.620)	(0.615)	(0.616)
PostSD × Time	0.123*	0.130*	0.125*	0.050	0.048
	(0.052)	(0.052)	(0.052)	(0.051)	(0.051)
PostSD × REL_PGI	0.455		0.502	0.347	0.259
	(0.849)		(0.846)	(0.841)	(0.844)
DEP_PGI		−2.140***	−2.087***	−1.726**	−1.801**
		(0.614)	(0.615)	(0.609)	(0.611)
PostSD × DEP_PGI		1.069	1.053	0.995	1.113
		(0.854)	(0.852)	(0.843)	(0.846)
CESD_scale				−2.229***	−1.802***
				(0.207)	(0.336)
PostSD × CESD_scale					−0.703+
					(0.423)
Num.Obs.	7911	7911	7911	7911	7911
R2	0.043	0.040	0.045	0.062	0.062
R2 Adj.	0.042	0.039	0.044	0.061	0.061
AIC	78 755.7	78 778.7	78 741.4	78 604.1	78 602.7
BIC	78 825.5	78 848.5	78 825.1	78 694.8	78 700.3
RMSE	33.14	33.21	33.13	32.88	32.87

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

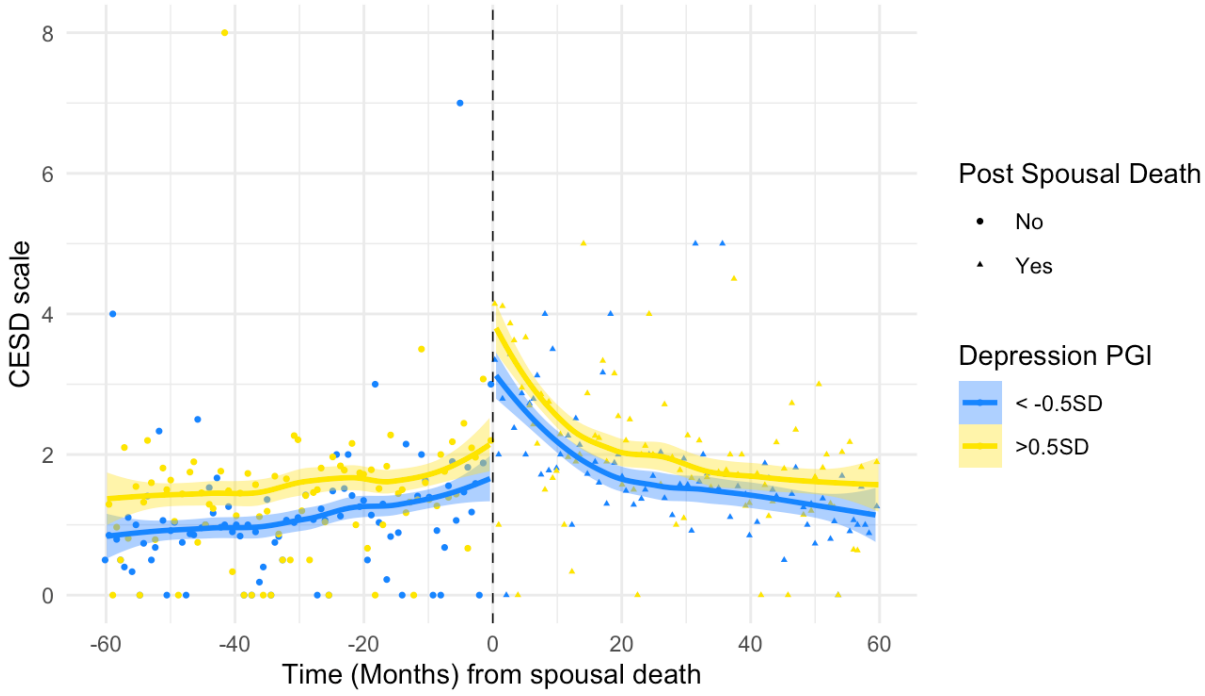
The trajectories for depressive symptoms have a different pattern, with slowly increasing CESD scores before spousal death and a more drastically declining trend after a big "jump" of CESD scores right after the death. The non-parametric local polynomial regressions fit

smooth curves, showing similar trajectories of two parallel lines of high and low depression PGI in Figure 4.2.3 and high and low religious attendance PGI in Figure 4.2.4, respectively. The separation of the parallel lines of high and low religious attendance with almost zero overlaps after the spousal death can be observed in Figure 4.2.5, indicating substantial protective effects of religious attendance on depression. Models 4 and 5 in Table 4.2.6 also demonstrate the significance of the negative association between religious attendance and depressive symptoms after controlling for both depression PGI and religious attendance PGI and other covariates. The interaction term between the PostSD indicator and religious attendance is also significantly negative, which suggests a greater protective effect for bereavement after spousal death.

Table 4.2.6 illustrates the trajectories of depressive symptoms over time following spousal death. The PostSD indicator has a positive coefficient, while the interaction term between the PostSD indicator and interview time has a negative coefficient, indicating a decrease in depressive symptoms over time following spousal death. Older males with higher education are more likely to report fewer depressive symptoms. Depression PGI positively predicts CESD scores, while religious attendance negatively predicts CESD scores. Both of their interaction terms with the PostSD indicator are not statistically significant, which supports the parallel trends observed in the figures. Tables B.8 and B.9 in the Supplementary Materials

using the NLS model also have non-significant γ coefficients, indicating no genetic heterogeneity of decay rates after death. NLS models show a positive main effect (β_2) of death on depressive symptoms and a large population average decay rate (λ) of nearly 7 over time. β_3 for the depression PGI is significantly positive, meaning that respondents with a higher genetic predisposition to depression are more likely to have a higher increase of symptoms right after the spousal death than those with a lower depression PGI. Figures using local linear regression to fit trajectories are available in Supplementary Materials Figures B.1-B.7.

Figure 4.2.3 Trajectories of depressive symptoms for HRS respondents with a high depression PGI and a low depression PGI - (local polynomial regression)[21]



[21] Trajectories for respondents with a high depression PGI are graphed in yellow (more than 0.5 standard deviations above the mean, N=778, obs = 2,848), while those with low depression PGI are graphed in blue (more than 0.5 standard deviations below the mean, N=771, obs = 2,805).

Figure 4.2.4 Trajectories of depressive symptoms for HRS respondents with a high religious attendance (REL) PGI and a low REL PGI - (local polynomial regression) [22]

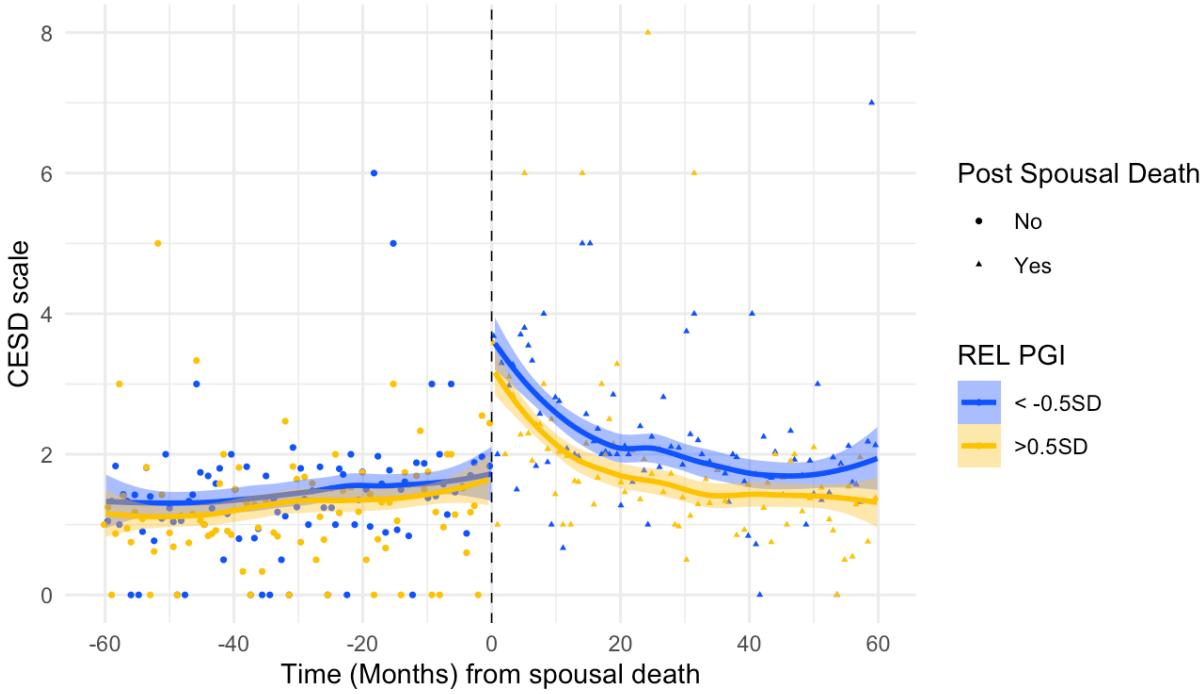


Figure 4.2.5 Trajectories of depressive symptoms for HRS respondents with different levels of religious attendance - (local polynomial regression) [23]

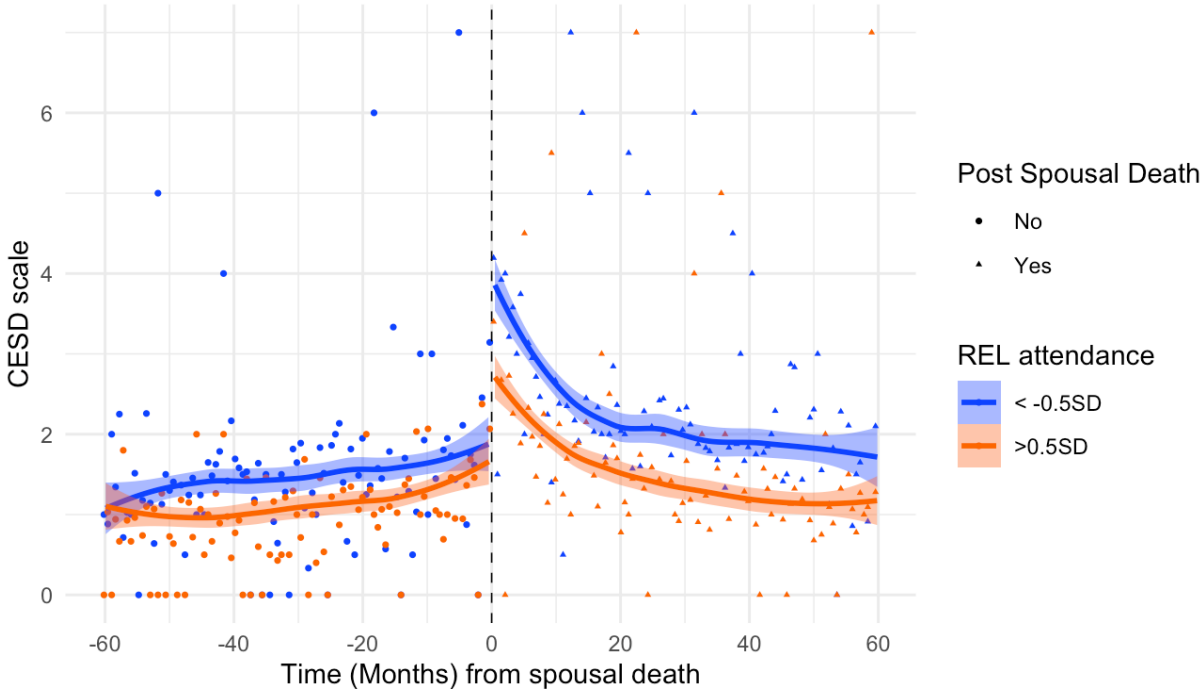


Table 4.2.6 Linear models predicting depressive symptoms (8-item CESD score) among non-Hispanic white HRS respondents interviewed within the 120-month window [N = 2,437, obs = 7,911] of spousal death, with genotypic data

	CESD [8-item] Model1	Model2	Model3	Model4	Model5
(Intercept)	3.649***	3.636***	3.557***	3.522***	3.439***
	(0.266)	(0.266)	(0.265)	(0.263)	(0.263)
GenderMale	−0.141**	−0.153**	−0.147**	−0.231***	−0.230***
	(0.054)	(0.054)	(0.054)	(0.055)	(0.054)
Age	−0.009**	−0.009**	−0.009**	−0.005+	−0.005+
	(0.003)	(0.003)	(0.003)	(0.003)	(0.003)
Edyears	−0.102***	−0.100***	−0.097***	−0.093***	−0.093***
	(0.010)	(0.010)	(0.010)	(0.010)	(0.010)
PostSD	0.966***	0.972***	0.962***	0.975***	1.161***
	(0.106)	(0.106)	(0.106)	(0.106)	(0.119)
Time	0.011***	0.011***	0.011***	0.011***	0.011***
	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)
DEP_PGI	0.163***		0.162***	0.145***	0.152***
	(0.034)		(0.034)	(0.034)	(0.034)
PostSD × Time	−0.034***	−0.034***	−0.034***	−0.033***	−0.033***
	(0.003)	(0.003)	(0.003)	(0.003)	(0.003)
PostSD × DEP_PGI	−0.025		−0.026	−0.018	−0.027
	(0.050)		(0.050)	(0.050)	(0.050)
REL_PGI		−0.077*	−0.073*	−0.056+	−0.062+
		(0.034)	(0.033)	(0.033)	(0.033)
PostSD × REL_PGI		−0.067	−0.069	−0.065	−0.050
		(0.050)	(0.050)	(0.050)	(0.050)
attend_REL				−0.008***	−0.005***
				(0.001)	(0.001)
PostSD × attend_REL					−0.005***
					(0.001)
Num.Obs.	7911	7911	7911	7911	7911
R2	0.075	0.073	0.078	0.094	0.096
R2 Adj.	0.074	0.072	0.077	0.093	0.095
AIC	34 058.6	34 077.1	34 036.8	33 899.5	33 883.6
BIC	34 128.4	34 146.9	34 120.5	33 990.2	33 981.3
RMSE	1.97	1.98	1.97	1.95	1.95

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

5. Discussion

This study employed a quasi-experimental framework to investigate gene-environment interactions manifested as varying depressive and religious responses to adverse events in two American populations. The effects of the 9/11 terrorist attacks on young American adults differ significantly from those of spousal death on elderly Americans. The increase in

depressive symptoms was more pronounced for individuals experiencing the personal loss of a loved one. The aggregated 9-item CESD score among Add Health respondents did not rise as sharply as the reporting of a single item of feeling sad following the 9/11 attacks. This suggests that the collective trauma of 9/11 had a more moderate impact on overall depression levels compared to the intense and prolonged grief experienced after spousal death. Religious attendance also shifted following adverse events. In the wake of the 9/11 attacks, many people turned to religion for solace and support, reflecting a common coping mechanism for dealing with collective trauma. On the other hand, those who experienced spousal death might seek comfort in religious communities, drawing on their faith to navigate through personal grief and loss. In summary, the results of this study illuminate the differences in depressive and religious responses to the distinct adverse events of receiving news of the 9/11 attacks and experiencing spousal death. The findings underscore the importance of considering both the nature of the trauma and the population affected when examining gene-environment interactions related to mental health and coping mechanisms.

The intriguing finding of the gene-environment interaction on religious attendance reveals that individuals with varying genetic predispositions toward religious attendance may react differently to external stressors. In the case of Add Health respondents with a high religious attendance PGI, their participation in religious activities saw a substantial increase following

the 9/11 attacks. These results imply that adverse events, such as the 9/11 attacks, can lead to heightened religious attendance even among less religious generations of Americans. The genetic heterogeneity of this effect among younger Americans suggests that, as society becomes more secular, those with a stronger genetic inclination toward religious attendance might be more likely to turn to religion as a coping mechanism in the face of adversity. This highlights the complex interplay between genetics, environmental factors, and the role of religion in helping individuals navigate through difficult times.

Other genetic heterogeneities on depression and religious attendance have been demonstrated in parallel trajectories, indicating that the main effects of polygenic indexes (PGIs) on the outcome variables remain unchanged following adverse events. High religious attendance PGI and low depression PGI have been shown to be protective against depression. In the Add Health data, the two PGIs are correlated, suggesting that gene-gene interactions pose additional challenges in excluding confounders of social outcomes for causal inference. The genetic predispositions toward religious attendance and depression may be interconnected, with shared genetic factors influencing both traits and their interplay with environmental stressors. The presence of the significant PGI correlation in the context of depression and religious attendance highlights the complexity of disentangling the genetic and environmental factors contributing to these outcomes, as also shown in genomic SEM analysis in Chapter 1.

To better understand the causal relationships, researchers may need to employ advanced statistical methods and utilize large samples to account for potential confounders and shared genetic architectures.

Both of the analyses have shown direct protective effects of religious attendance on depressive outcomes after controlling for genetic factors. With the differential responses to religious attendance after 9/11, the results support the mixed effects hypothesis that religiosity has both direct and buffering effects on mental health. However, the reverse causation cannot be teased out using the current research design, as the association can be explained by those with more depressive symptoms being more likely to attend religious activities for social support and spiritual guidance.

The observed correlation between religious attendance and depressive symptoms highlights the importance of considering religious factors in any research investigating mental health. Neglecting the impact of religious attendance may lead to the violation of essential assumptions, such as the similarity of unobserved and observed predictors in proximity to the cutoff point within a regression discontinuity design examining depressive symptoms (Fletcher, 2014). This consideration is critical to avoid potential biases in the analysis and interpretation of study results. Although the previous candidate gene discovery of gene-

environment (GxE) effects was not replicated in this study, employing PGI as genome-wide predictors demonstrates that gene-gene interactions frequently act as confounding variables for commonly investigated social factors. In the Health and Retirement Study (HRS), both genetic components were found to be significant predictors of religious attendance and depressive outcomes. Relying solely on phenotypic traits for causal claims may be problematic due to the presence of unobserved genetic confounders. It is essential to account for these genetic influences in order to improve the validity of study results. With the increasing availability of genetic data, social scientists now have the opportunity to integrate this information into their research, enabling them to account for genetic influences and further explore the complex interplay between genes and environments.

Our analyses were limited to non-Hispanic whites with genotyping data, which represents a relatively small subsample of the larger nationally representative samples. The statistical power was further limited due to the scarce availability of questionnaire data about religiosity, which may reduce our ability to detect small interaction effects. The implication of the results in this chapter may vary across different racial and ethnic groups with different genetic ancestries. This chapter focused on two specific adverse life events - spousal death and the 9/11 attacks - due to the availability of data that allowed for investigation of causal effects. However, it is important to note that the results may not be generalizable to other

types of adverse events. Future research can examine gene-environment interactions using other types of environmental changes. Additionally, while religious attendance was used as a proxy for studying religiosity in this study, this neglects the nuances of different religious teachings regarding death and bereavement. This limitation suggests that future studies can investigate religiosity using a more comprehensive approach combining various measurements of religiosity.

The field of gene-environment interplay is continuously advancing with larger-scale genome-wide association studies on more diverse populations and more precise genetic measurements with better predictive power. This study's main contribution is to suggest that religious attendance, or similar forms of social support, may serve as a buffer for adverse life events that can cause depressive symptoms. Moreover, the impact of religious attendance may vary across individuals with different genetic backgrounds. Those with a higher religious attendance PGI may find attending religious activities a more effective coping strategy for dealing with stressful life events. Therefore, future research on the gene-environment interplay in psychiatry should consider religiosity both for explanatory and therapeutic purposes.

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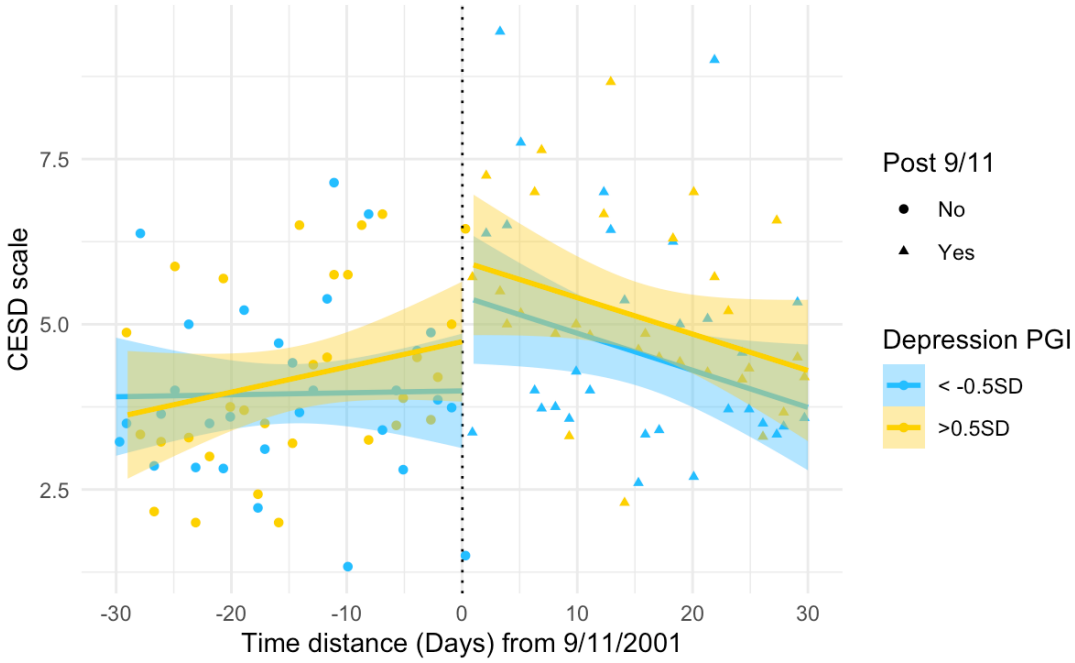
Chapter 3 Supplementary Materials

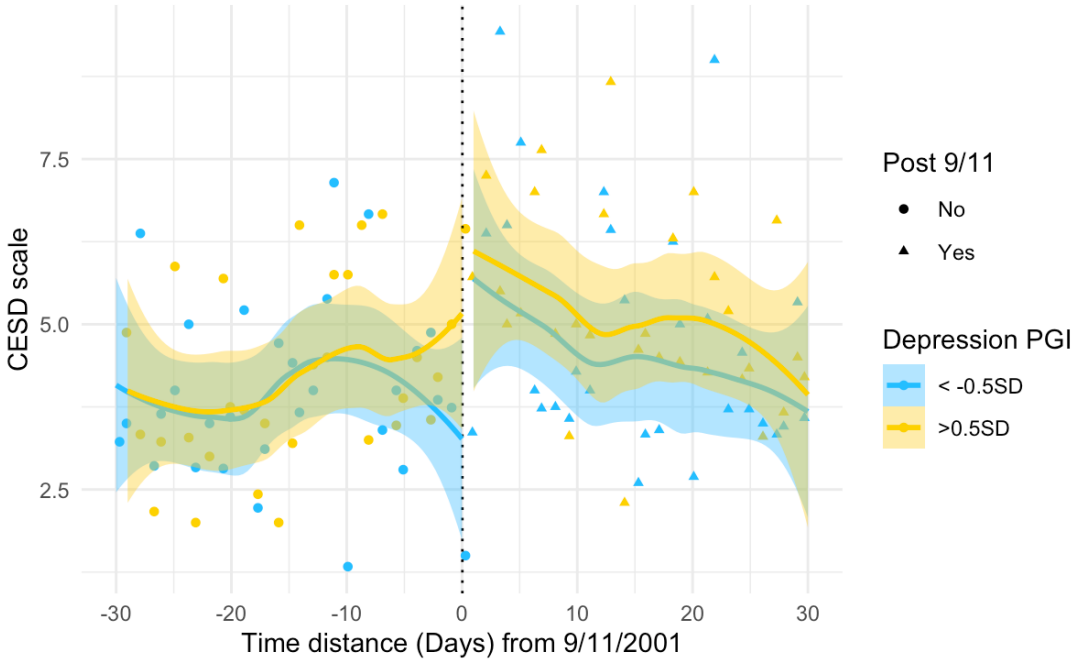
A. Responses to 9/11: Evidence from the Add Health study

Table A.1 Add Health descriptive statistics, non-Hispanic whites interviewed at Wave 3 with genotypic data and complete observations [N = 4,862]

Variable	Mean	SD	Range
Gender - Female	0.54	Binary	[0, 1]
Age	21.84	1.75	[18, 27]
Years of education	13.23	1.95	[6, 22]
Region - Northeast	0.13	Binary	[0, 1]
Region - South	0.34	Binary	[0, 1]
Region - West	0.17	Binary	[0, 1]
After 9/11 indicator	0.77	Binary	[0, 1]
Interview Date centered around 9/11	61.46	68.00	[-146, 221]
CESD scale [9-item]	4.27	3.91	[0, 24]
Sadness	0.51	0.66	[0, 3]
Depression PGI	-0.02	0.99	[-4.31, 3.18]
Religious attendance [times/year]	14.79	23.54	[0, 90]
Religious attendance [>= weekly]	0.15	Binary	[0, 1]
Religious attendance PGI	0.04	1.00	[-3.46, 4.45]

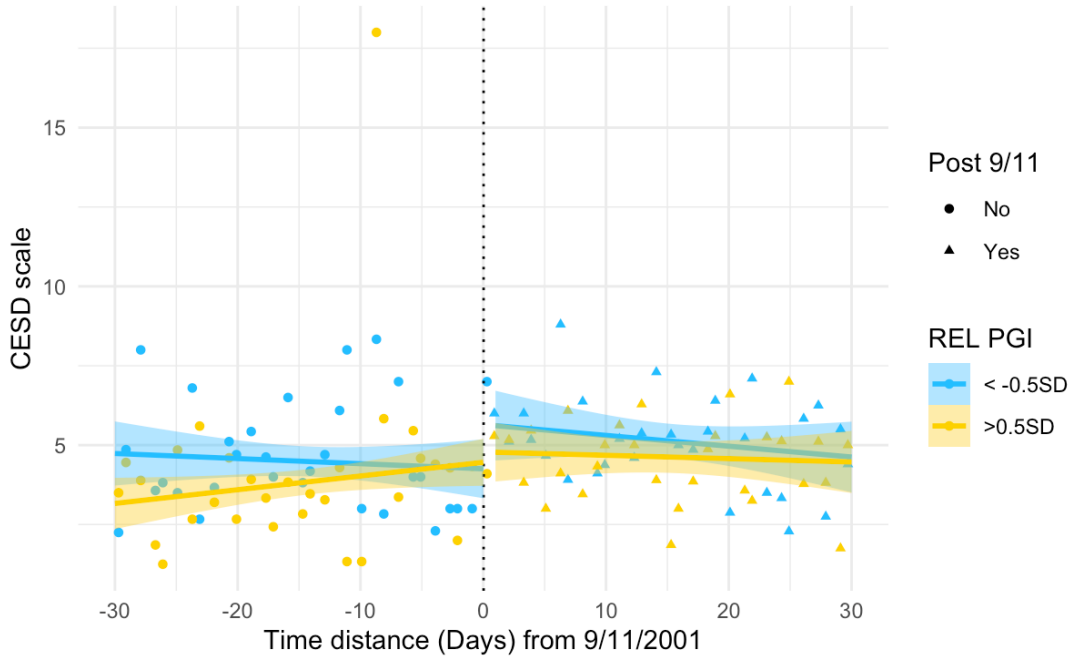
Figure A.2.a & A.2.b Trajectories of depressive symptoms for Add Health respondents with a high depression PGI and a low depression PGI (local linear regression & local polynomial regression) [24]

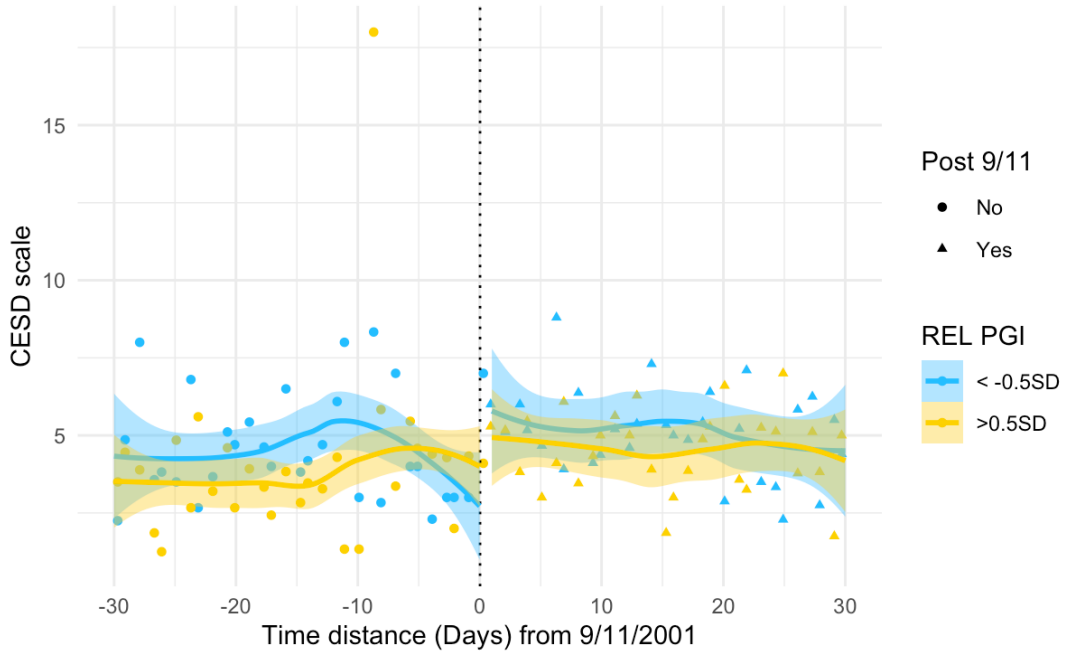




[24] Trajectories for respondents with a high depression PGI are graphed in yellow (more than 0.5 standard deviations above the mean, N=500), while those with a low PGI are graphed in blue (more than 0.5 standard deviations below the mean, N=536).

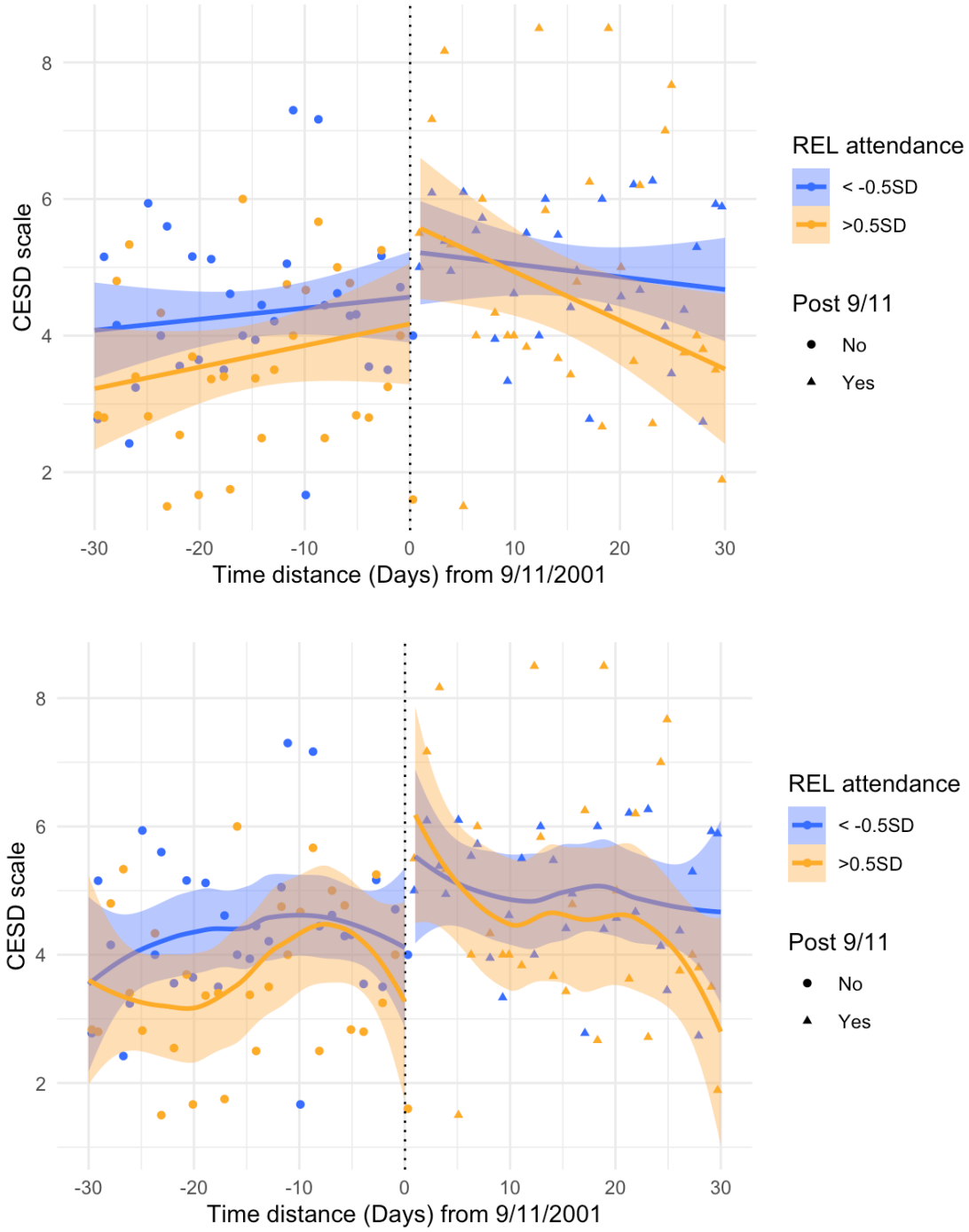
Figure A.3.a & A.3.b Trajectories of depressive symptoms for Add Health respondents with a high religious attendance PGI and a low religious attendance PGI (local linear regression & local polynomial regression) [25]





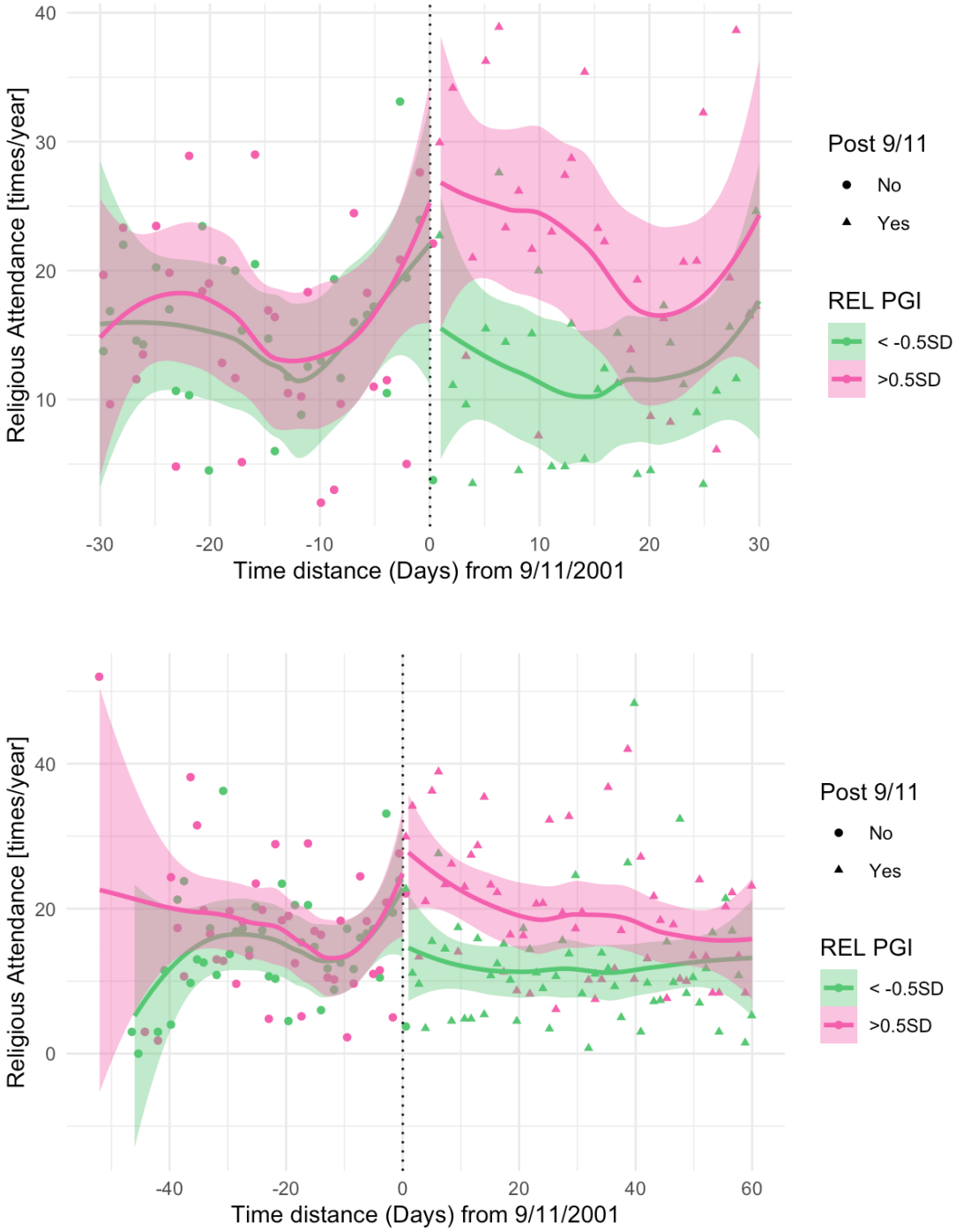
[25] Trajectories for respondents with high a religious attendance PGI are graphed in yellow (more than 0.5 standard deviations above the mean, N=564), while those with a low PGI are graphed in blue (more than 0.5 standard deviations below the mean, N=519).

Figure A.4.a & A.4.b Trajectories of depressive symptoms for Add Health respondents with different levels of religious attendance (local linear regression & local polynomial regression) [26]



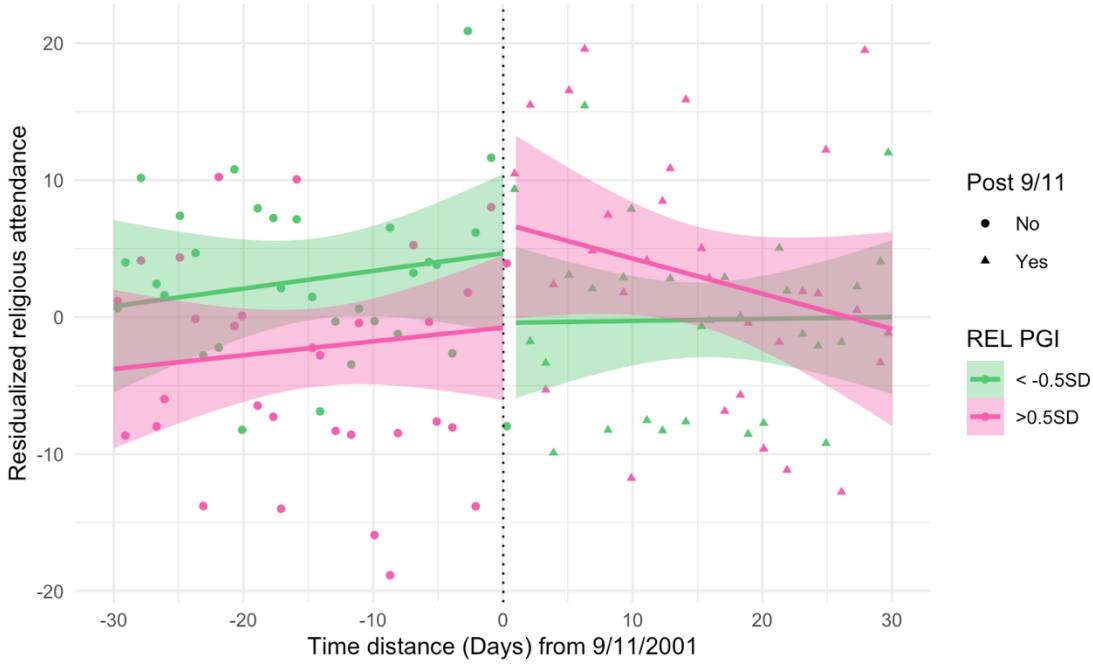
[26] Trajectories for respondents with more frequent religioius attendance are graphed in orange (more than 0.5 standard deviations above the mean, N=435), while those with less frequent religious attendancare graphed in blue (more than 0.5 standard deviations below the mean, N=982).

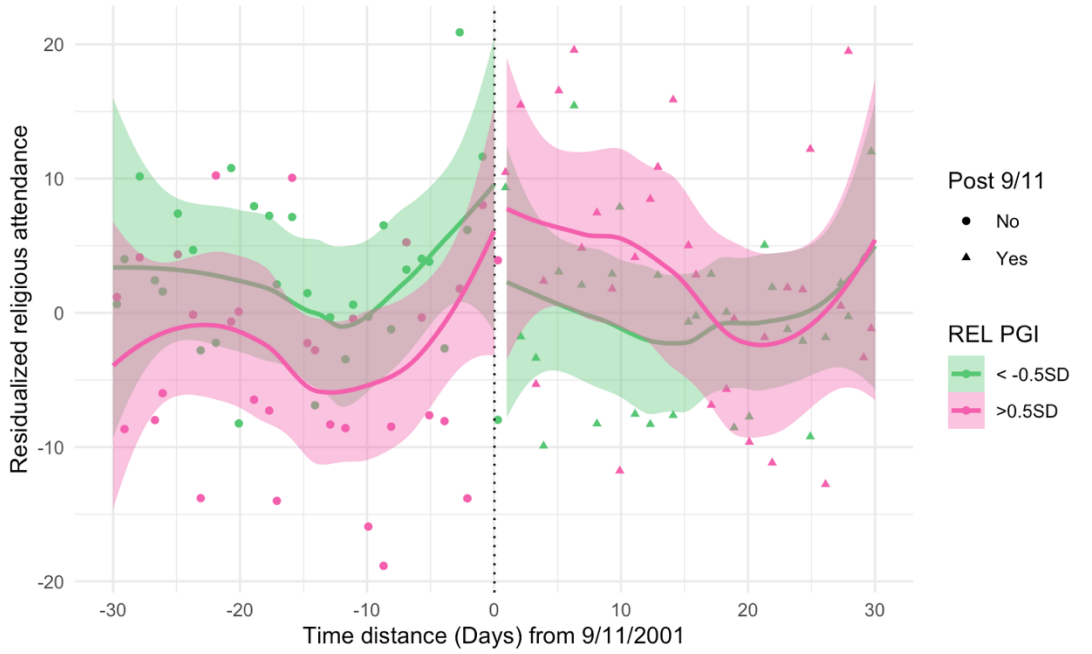
Figure A.5.a & A.5.b Trajectories of religious attendance for Add Health respondents with a high religious attendance (REL) PGI and a low REL PGI within 60 days versus 120 days of 9/11 attacks - (local polynomial regression) [27]



[27]Trajectories for respondents with a high religious attendance PGI are graphed in red (more than 0.5 standard deviations above the mean, N = 564 [60 days], N = 883 [120 days]), while those with a low PGI are graphed in green (more than 0.5 standard deviations below the mean, N=519 [60 days], N=788 [120 days]).

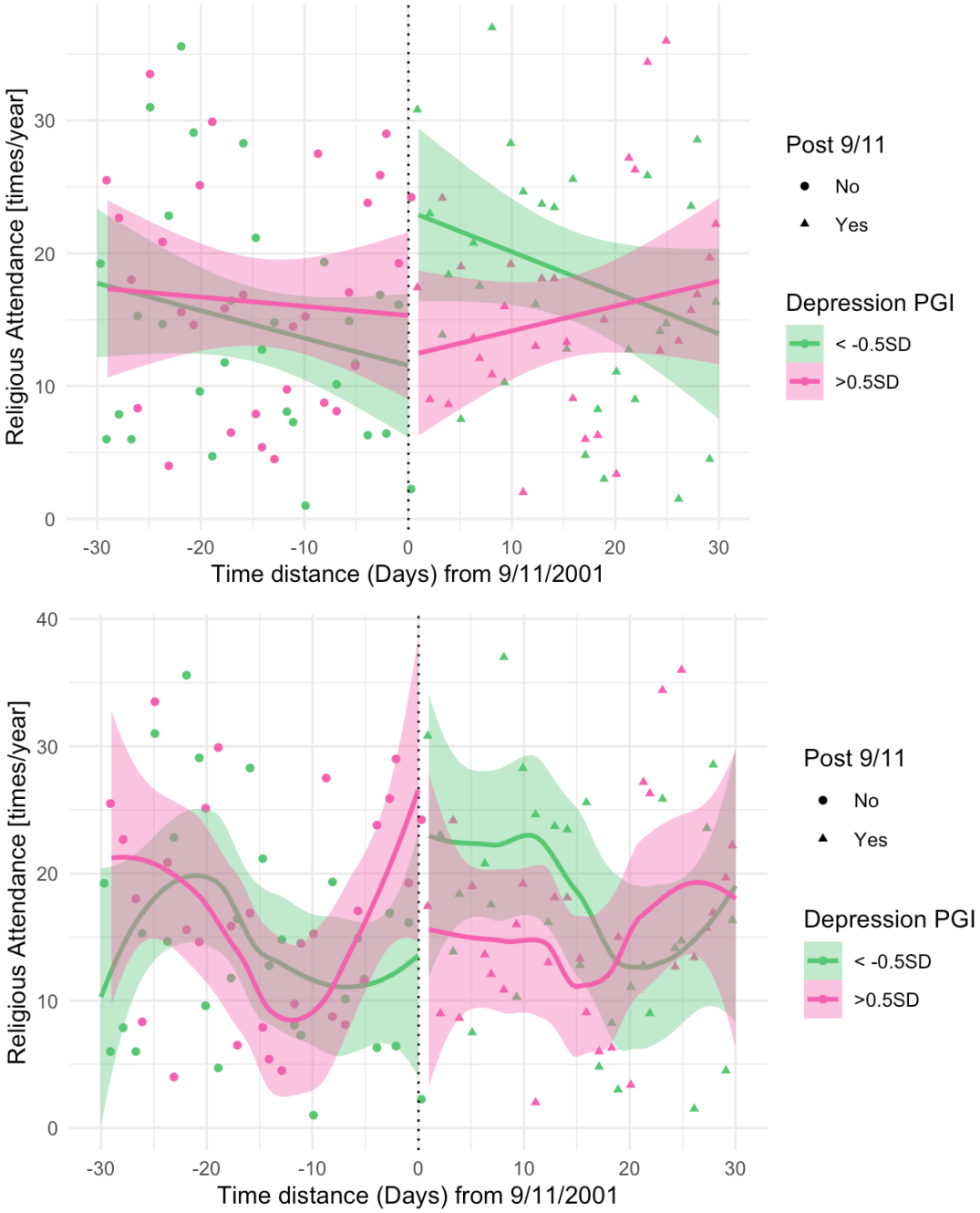
Figure A.5.c & A.5.d Trajectories of religious attendance residualized on REL PGI for Add Health respondents with a high REL PGI and a low REL PGI within 60 days of 9/11 attacks - (local linear regression & local polynomial regression) [28]





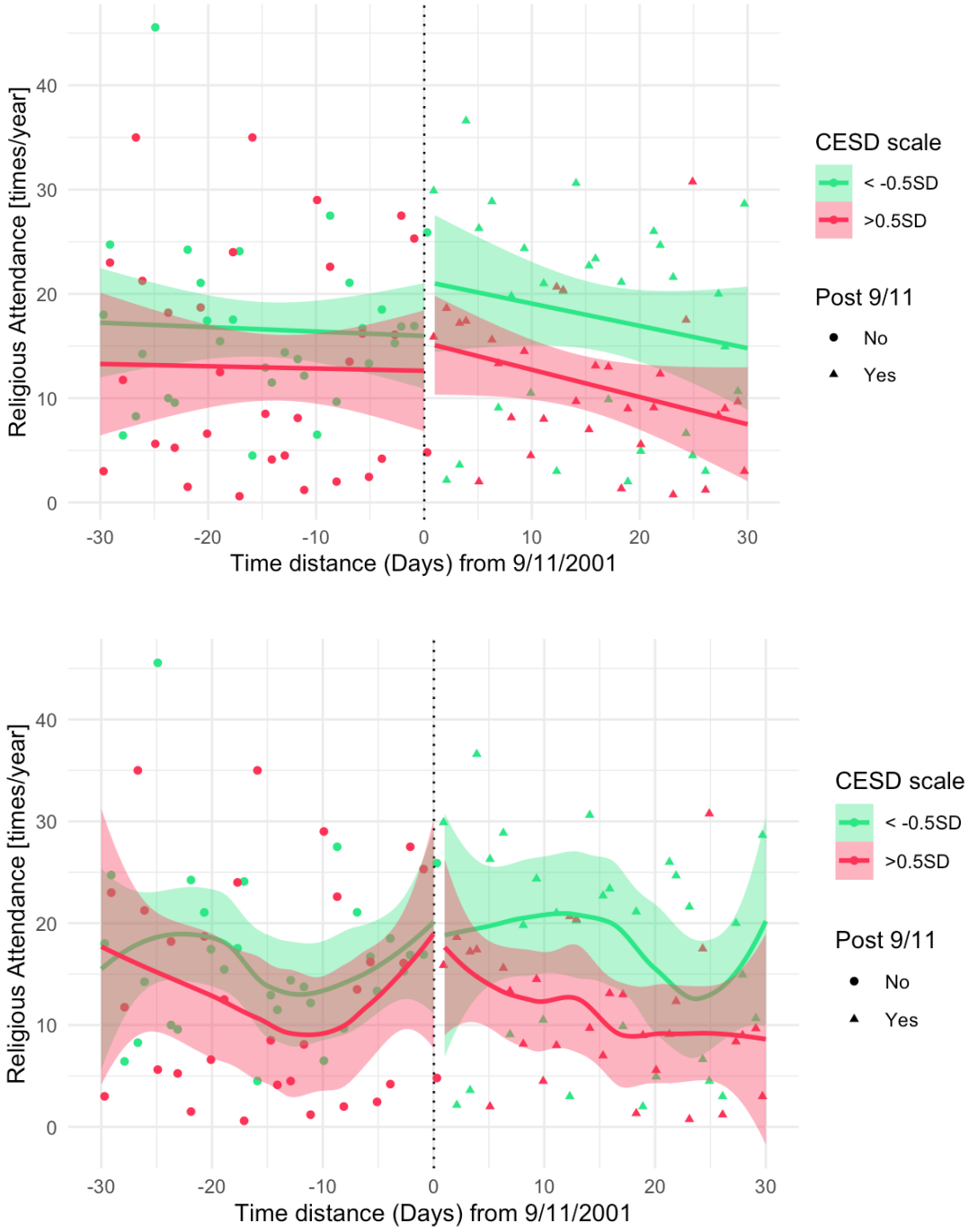
[28]Trajectories for respondents with a high religious attendance PGI are graphed in red (more than 0.5 standard deviations above the mean, N = 564 [60 days], N = 883 [120 days]), while those with a low PGI are graphed in green (more than 0.5 standard deviations below the mean, N=519 [60 days], N=788 [120 days]).

Figure A.6.a. & A.6.b Trajectories of religious attendance for Add Health respondents with a high depression PGI and a low depression PGI - (local linear regression & local polynomial regression) [29]



[29] Trajectories for respondents with a high depression PGI are graphed in red (more than 0.5 standard deviations above the mean, N=500), while those with a low PGI are graphed in green (more than 0.5 standard deviations below the mean, N=536).

Figure A.7.a. & A.7.b Trajectories of religious attendance for Add Health respondents with a high standardized CESD score and a low CESD score - (local linear regression & local polynomial regression) [30]



[30] Trajectories for respondents with a high CESD score are graphed in red (more than 0.5 standard deviations above the mean, N=418), while those with a low CESD score are graphed in green (more than 0.5 standard deviations below the mean, N=658).

Table A.8.a Linear models predicting CESD score [9-item] among non-Hispanic whites interviewed at Wave 3 with genotypic data and complete observations [N = 4,862]

	CESD [9-item] Model1	Model2	Model3	Model4	Model5
(Intercept)	7.408***	7.362***	7.377***	7.419***	7.435***
	(0.734)	(0.734)	(0.735)	(0.735)	(0.738)
GenderMale	−1.025***	−1.022***	−1.018***	−1.038***	−1.037***
	(0.111)	(0.110)	(0.110)	(0.111)	(0.111)
Age	0.072*	0.070*	0.069*	0.065*	0.066*
	(0.032)	(0.032)	(0.032)	(0.032)	(0.032)
Edyears	−0.326***	−0.321***	−0.319***	−0.310***	−0.310***
	(0.030)	(0.030)	(0.030)	(0.030)	(0.030)
RegionNortheast	0.405*	0.428*	0.408*	0.390*	0.389*
	(0.176)	(0.177)	(0.176)	(0.176)	(0.177)
RegionSouth	−0.145	−0.138	−0.149	−0.099	−0.100
	(0.133)	(0.132)	(0.133)	(0.133)	(0.133)
RegionWest	0.120	0.128	0.123	0.129	0.130
	(0.163)	(0.163)	(0.162)	(0.162)	(0.162)
Post911	0.479*	0.479*	0.480*	0.484*	0.452+
	(0.239)	(0.241)	(0.241)	(0.240)	(0.258)
Time	0.000	0.000	0.000	0.000	0.000
	(0.009)	(0.010)	(0.010)	(0.010)	(0.010)
DEP_PGI	0.098		0.090	0.094	0.096
	(0.120)		(0.120)	(0.120)	(0.120)
Post911 × Time	−0.005	−0.005	−0.005	−0.005	−0.005
	(0.010)	(0.010)	(0.010)	(0.010)	(0.010)
Post911 × DEP_PGI	0.028		0.031	0.025	0.024
	(0.134)		(0.135)	(0.134)	(0.134)
REL_PGI		−0.148	−0.143	−0.135	−0.133
		(0.107)	(0.108)	(0.107)	(0.108)
Post911 × REL_PGI		0.043	0.044	0.050	0.047
		(0.122)	(0.123)	(0.122)	(0.123)
attend_REL				−0.006*	−0.007+
				(0.002)	(0.004)
Post911 × attend_REL					0.002
					(0.005)
Num.Obs.	4862	4862	4862	4862	4862
R2	0.045	0.044	0.045	0.046	0.047
R2 Adj.	0.042	0.042	0.043	0.044	0.044
AIC	26 853.9	26 854.2	26 853.9	26 850.0	26 851.9
BIC	26 938.2	26 938.6	26 951.2	26 953.9	26 962.2
RMSE	3.82	3.82	3.82	3.82	3.82

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Table A.8.b Linear models predicting sadness among non-Hispanic whites interviewed surrounding the 60-day window [N = 1,710] of September 11, 2001, with genotypic data

	Sadness Model1	Model2	Model3	Model4	Model5
(Intercept)	0.610**	0.609**	0.609**	0.607**	0.606**
	(0.229)	(0.228)	(0.229)	(0.228)	(0.228)
GenderMale	−0.172***	−0.171***	−0.171***	−0.172***	−0.173***
	(0.033)	(0.033)	(0.033)	(0.033)	(0.033)
Age	0.000	−0.001	−0.001	−0.001	−0.001
	(0.010)	(0.010)	(0.010)	(0.010)	(0.010)
Edyears	−0.002	−0.001	−0.001	0.000	0.000
	(0.009)	(0.009)	(0.009)	(0.009)	(0.009)
RegionNortheast	0.059	0.058	0.058	0.056	0.056
	(0.054)	(0.054)	(0.054)	(0.054)	(0.054)
RegionSouth	−0.061	−0.062	−0.062	−0.060	−0.060
	(0.040)	(0.040)	(0.040)	(0.040)	(0.040)
RegionWest	−0.002	−0.002	−0.002	−0.002	−0.002
	(0.049)	(0.049)	(0.049)	(0.049)	(0.049)
Post911	0.371***	0.369***	0.369***	0.370***	0.377***
	(0.071)	(0.071)	(0.071)	(0.071)	(0.074)
Time	0.002	0.002	0.002	0.002	0.002
	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)
DEP_PGI	0.002		0.001	0.001	0.001
	(0.024)		(0.024)	(0.024)	(0.024)
Post911 × Time	−0.015***	−0.015***	−0.015***	−0.015***	−0.015***
	(0.004)	(0.004)	(0.004)	(0.004)	(0.004)
Post911 × DEP_PGI	−0.003		−0.002	−0.002	−0.002
	(0.036)		(0.036)	(0.036)	(0.036)
REL_PGI		−0.022	−0.022	−0.021	−0.022
		(0.019)	(0.020)	(0.020)	(0.020)
Post911 × REL_PGI		0.021	0.021	0.022	0.024
		(0.032)	(0.032)	(0.032)	(0.032)
attend_REL				0.000	0.000
				(0.001)	(0.001)
Post911 × attend_REL					0.000
					(0.001)
Num.Obs.	1710	1710	1710	1710	1710
R2	0.050	0.050	0.050	0.051	0.051
R2 Adj.	0.044	0.044	0.043	0.043	0.042
AIC	3571.6	3570.7	3574.7	3576.5	3578.4
BIC	3642.4	3641.5	3656.3	3663.6	3670.9
RMSE	0.68	0.68	0.68	0.68	0.68

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Table A.9.a Linear models predicting religious attendance [times/year] among non-Hispanic whites interviewed surrounding the 120-day window [N = 2,672] of September 11, 2001, with genotypic data

	REL(120 Days) Model1	Model2	Model3	Model4	Model5
(Intercept)	6.022	5.342	5.888	7.851	8.014
	(6.329)	(6.358)	(6.332)	(6.385)	(6.449)
GenderMale	−3.023**	−2.991**	−3.019**	−3.326***	−3.327***
	(0.925)	(0.930)	(0.925)	(0.934)	(0.934)
Age	−0.525+	−0.584*	−0.521+	−0.509+	−0.508+
	(0.289)	(0.290)	(0.289)	(0.289)	(0.289)
Edyears	1.498***	1.648***	1.503***	1.432***	1.430***
	(0.237)	(0.238)	(0.238)	(0.239)	(0.239)
RegionNortheast	−4.027**	−3.934**	−4.051**	−3.994**	−3.990**
	(1.245)	(1.237)	(1.242)	(1.242)	(1.242)
RegionSouth	7.918***	7.825***	7.890***	7.798***	7.795***
	(1.137)	(1.144)	(1.137)	(1.136)	(1.137)
RegionWest	1.936	2.042	1.959	1.942	1.948
	(1.368)	(1.378)	(1.369)	(1.369)	(1.370)
Post911	1.139	1.186	1.127	1.354	1.092
	(1.814)	(1.831)	(1.812)	(1.814)	(2.162)
Time	0.019	0.017	0.018	0.019	0.019
	(0.063)	(0.063)	(0.063)	(0.063)	(0.063)
REL_PGI	1.225		1.280+	1.237	1.230
	(0.757)		(0.759)	(0.754)	(0.752)
Post911 × Time	−0.057	−0.054	−0.056	−0.062	−0.062
	(0.072)	(0.072)	(0.072)	(0.072)	(0.072)
Post911 × REL_PGI	1.916+		1.847+	1.853+	1.865+
	(0.978)		(0.980)	(0.977)	(0.973)
DEP_PGI		0.783	0.859	0.882	0.886
		(0.796)	(0.801)	(0.798)	(0.799)
Post911 × DEP_PGI		−1.162	−1.028	−1.019	−1.026
		(0.988)	(0.987)	(0.984)	(0.985)
CESD9				−0.264*	−0.299
				(0.112)	(0.186)
Post911 × CESD9					0.056
					(0.231)
Num.Obs.	2672	2672	2672	2672	2672
R2	0.059	0.049	0.059	0.061	0.061
R2 Adj.	0.055	0.045	0.054	0.056	0.056
AIC	24 528.5	24 556.5	24 531.0	24 528.0	24 529.9
BIC	24 605.0	24 633.0	24 619.4	24 622.2	24 630.0
RMSE	23.71	23.84	23.71	23.69	23.69

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

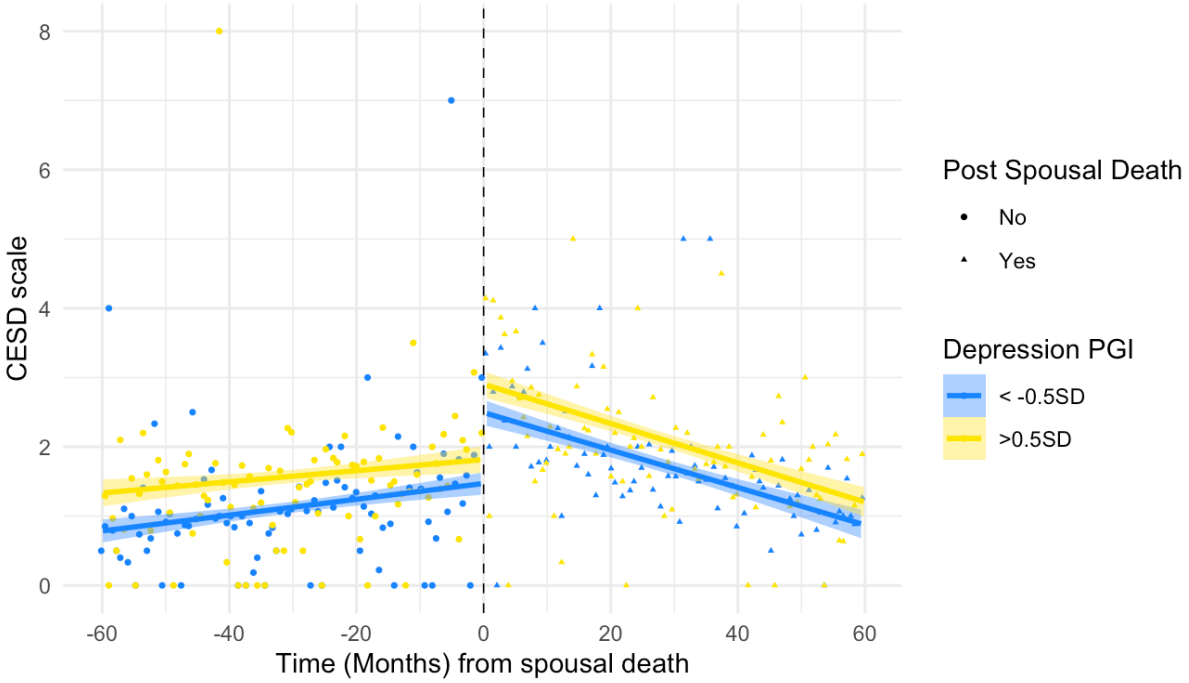
Table A.9.b Linear models predicting religious attendance [times/year] among non-Hispanic whites interviewed at Wave 3 with genotypic data and complete observations [N = 4,862]

	REL Model1	Model2	Model3	Model4	Model5
(Intercept)	7.373+	6.549	7.262	8.787*	9.193*
	(4.451)	(4.471)	(4.449)	(4.471)	(4.563)
GenderMale	−3.367***	−3.258***	−3.372***	−3.582***	−3.585***
	(0.655)	(0.658)	(0.655)	(0.664)	(0.664)
Age	−0.606**	−0.654**	−0.601**	−0.586**	−0.587**
	(0.199)	(0.200)	(0.199)	(0.199)	(0.199)
Edyears	1.534***	1.672***	1.535***	1.469***	1.469***
	(0.167)	(0.167)	(0.167)	(0.169)	(0.169)
RegionNortheast	−3.157***	−3.035***	−3.143***	−3.058***	−3.058***
	(0.827)	(0.829)	(0.827)	(0.828)	(0.828)
RegionSouth	8.476***	8.418***	8.480***	8.449***	8.441***
	(0.818)	(0.824)	(0.820)	(0.820)	(0.820)
RegionWest	1.068	1.175	1.094	1.119	1.121
	(0.957)	(0.961)	(0.957)	(0.957)	(0.957)
Post911	0.641	0.643	0.598	0.697	0.183
	(1.439)	(1.444)	(1.441)	(1.440)	(1.741)
Time	0.025	0.022	0.025	0.025	0.026
	(0.056)	(0.056)	(0.056)	(0.056)	(0.056)
REL_PGI	1.223		1.273+	1.243+	1.225
	(0.754)		(0.755)	(0.752)	(0.748)
Post911 × Time	−0.043	−0.040	−0.043	−0.044	−0.044
	(0.057)	(0.057)	(0.057)	(0.057)	(0.057)
Post911 × REL_PGI	1.036		0.971	0.980	1.003
	(0.843)		(0.845)	(0.842)	(0.838)
DEP_PGI		0.738	0.808	0.826	0.837
		(0.795)	(0.800)	(0.797)	(0.797)
Post911 × DEP_PGI		−1.124	−1.081	−1.075	−1.090
		(0.877)	(0.880)	(0.877)	(0.878)
CESD9				−0.207*	−0.298
				(0.087)	(0.185)
Post911 × CESD9					0.117
					(0.208)
Num.Obs.	4862	4862	4862	4862	4862
R2	0.065	0.058	0.066	0.067	0.067
R2 Adj.	0.063	0.056	0.063	0.064	0.064
AIC	44 208.9	44 245.7	44 211.0	44 207.2	44 208.8
BIC	44 293.3	44 330.0	44 308.4	44 311.0	44 319.2
RMSE	22.75	22.84	22.75	22.74	22.74

+ $p < 0.1$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

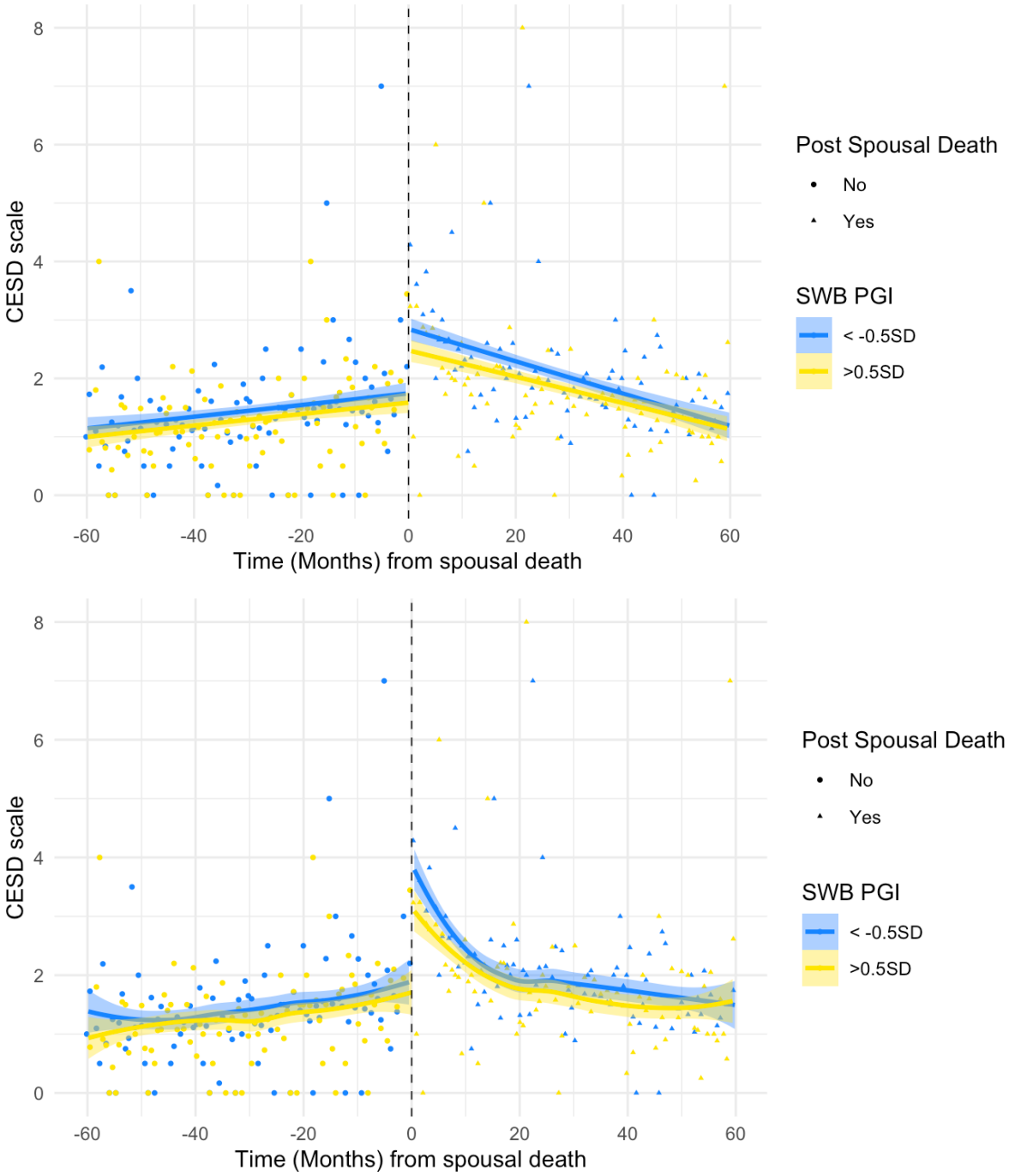
B. Responses to spousal death: Evidence from the HRS study

Figure B.1 Trajectories of depressive symptoms for HRS respondents with a high depression PGI and a low depression PGI - (local linear regression) [31]



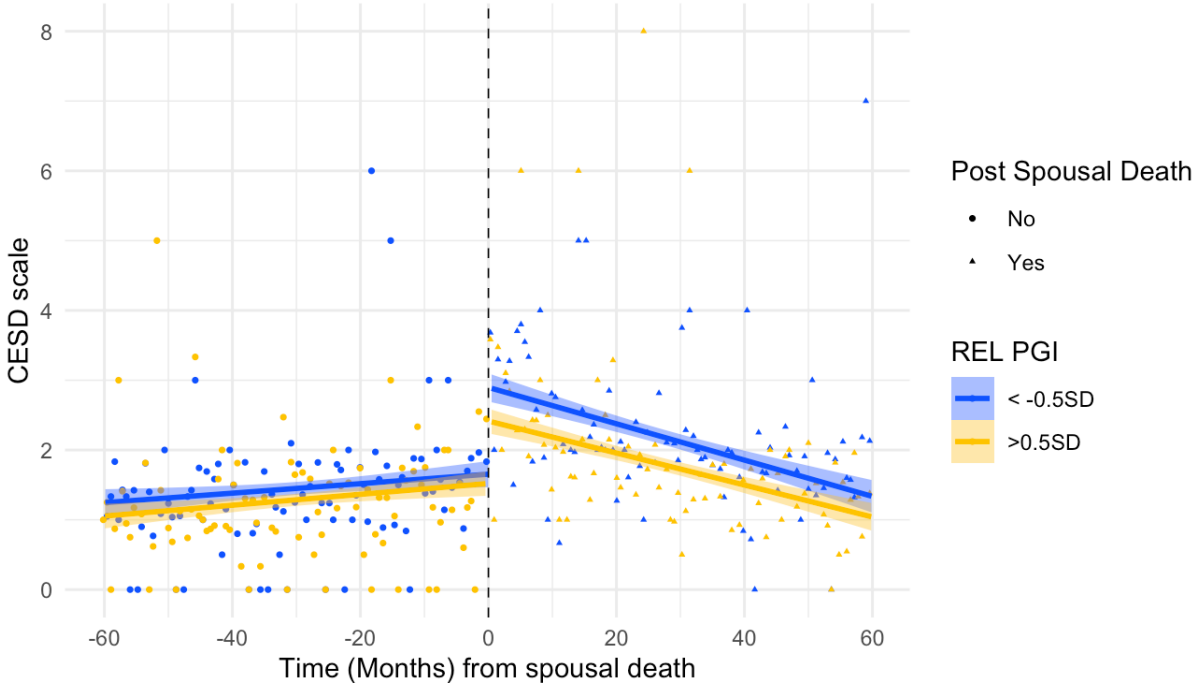
[31] Trajectories for respondents with a high depression PGI are graphed in yellow (more than 0.5 standard deviations above the mean, N=778, obs = 2,848), while those with a low PGI are graphed in blue (more than 0.5 standard deviations below the mean, N=771, obs = 2,805).

Figure B.2.a. & B.2.b Trajectories of depressive symptoms for HRS respondents with a high subjective well-being (SWB) PGI and a low SWB PGI - (local linear regression & local polynomial regression) [32]



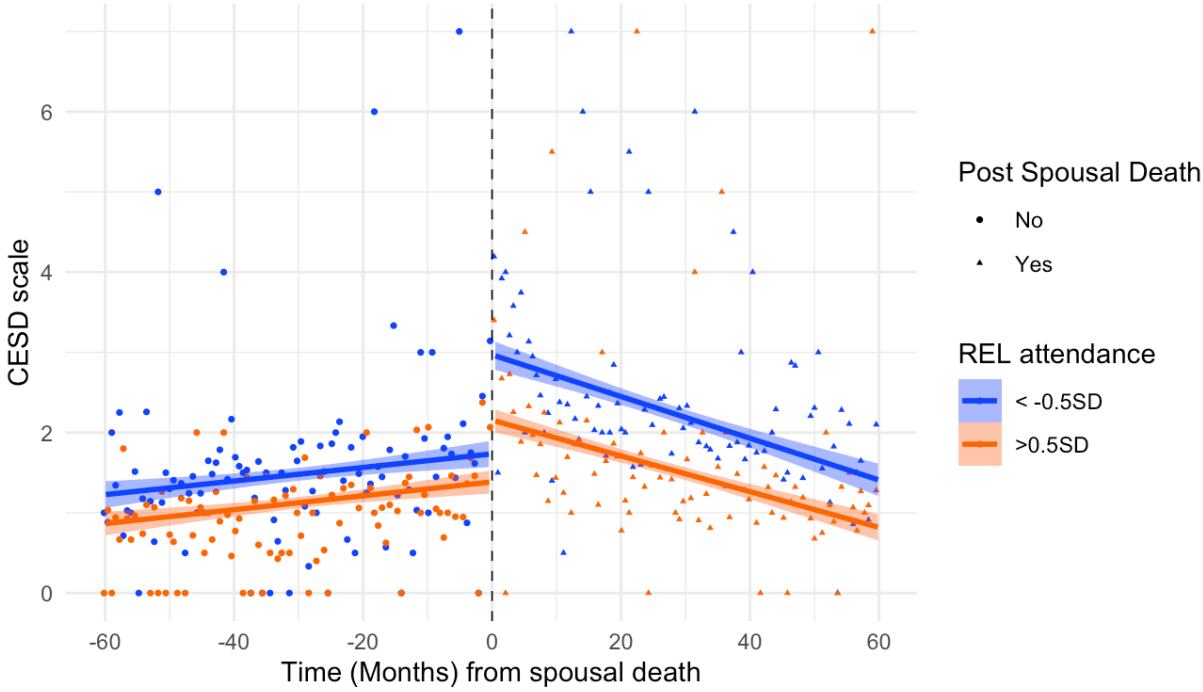
[32] Trajectories for respondents with a high subjective well-being PGI are graphed in yellow (more than 0.5 standard deviations above the mean, N=742, obs = 2,742), while those with a low PGI are graphed in blue (more than 0.5 standard deviations below the mean, N=771, obs = 2,823).

Figure B.3 Trajectories of depressive symptoms for HRS respondents with a high religious attendance (REL) PGI and a low REL PGI - (local linear regression) [33]



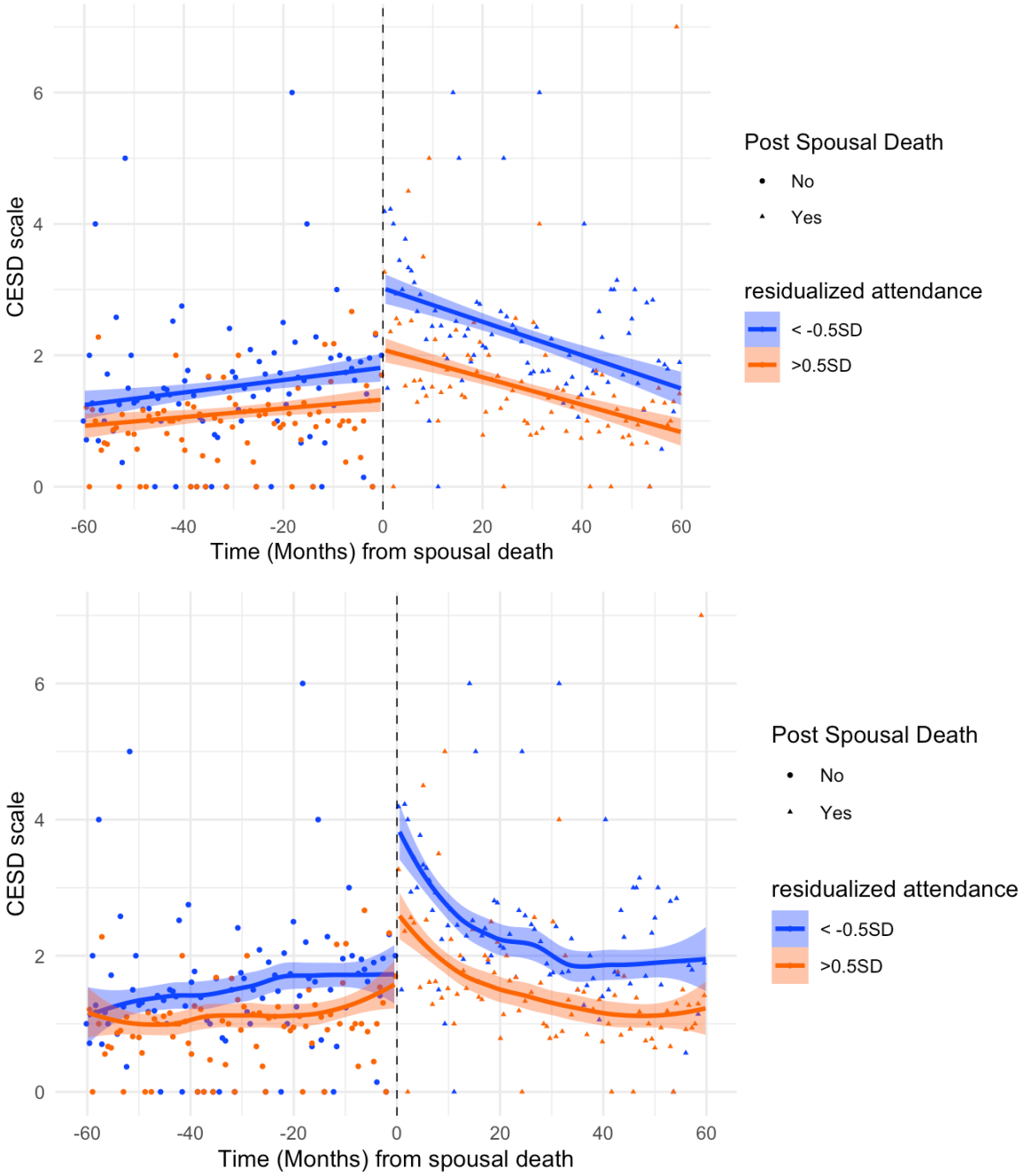
[33] Trajectories for respondents with a high religiosity PGI are graphed in yellow (more than 0.5 SD above the mean, N=755, obs = 2,803), while those with a low PGI are graphed in blue (more than 0.5 SD below the mean, N=759, obs = 2,817).

Figure B.4.a Trajectories of depressive symptoms for HRS respondents with different levels of religious attendance - (local linear regression) [34]



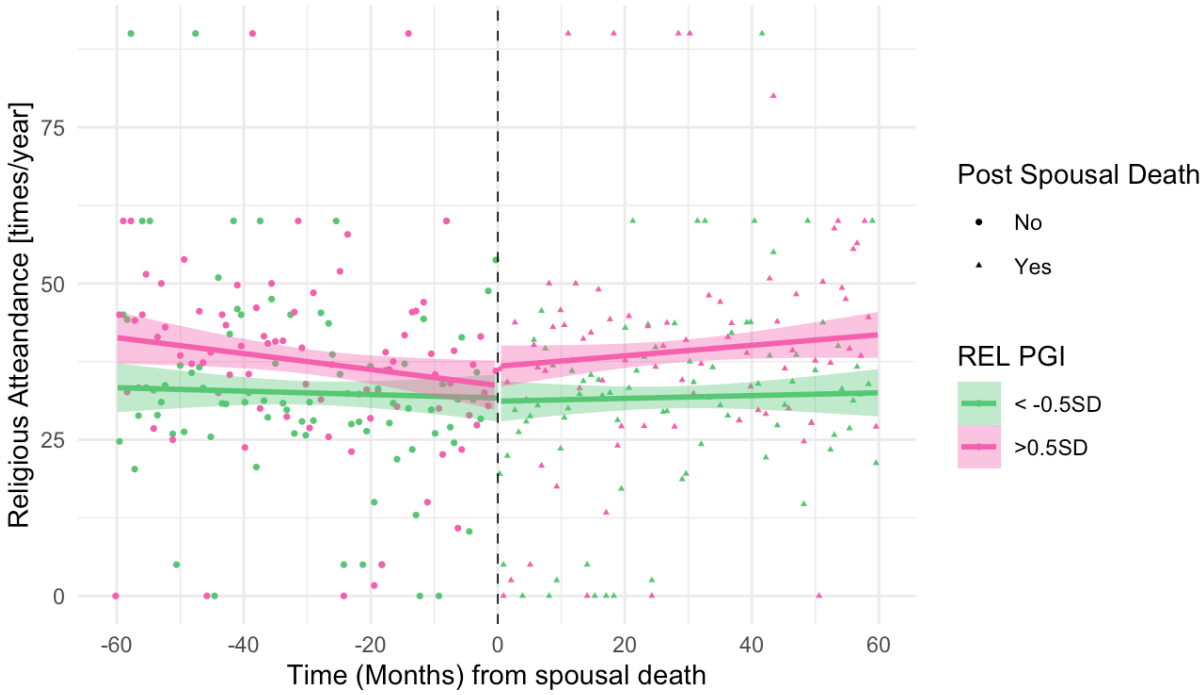
[34] Trajectories for respondents with more frequent religious attendance are graphed in orange (more than 0.5 SD above the mean, N=1,345, obs = 3,546), while those with less frequent religious attendance are graphed in blue (more than 0.5 SD below the mean, N=1,322, obs = 3,517).

Figure B.4.b & B.4.c Trajectories of depressive symptoms for HRS respondents with different levels of religious attendance residualized on religious attendance PGI - (local linear regression & local polynomial regression)[35]



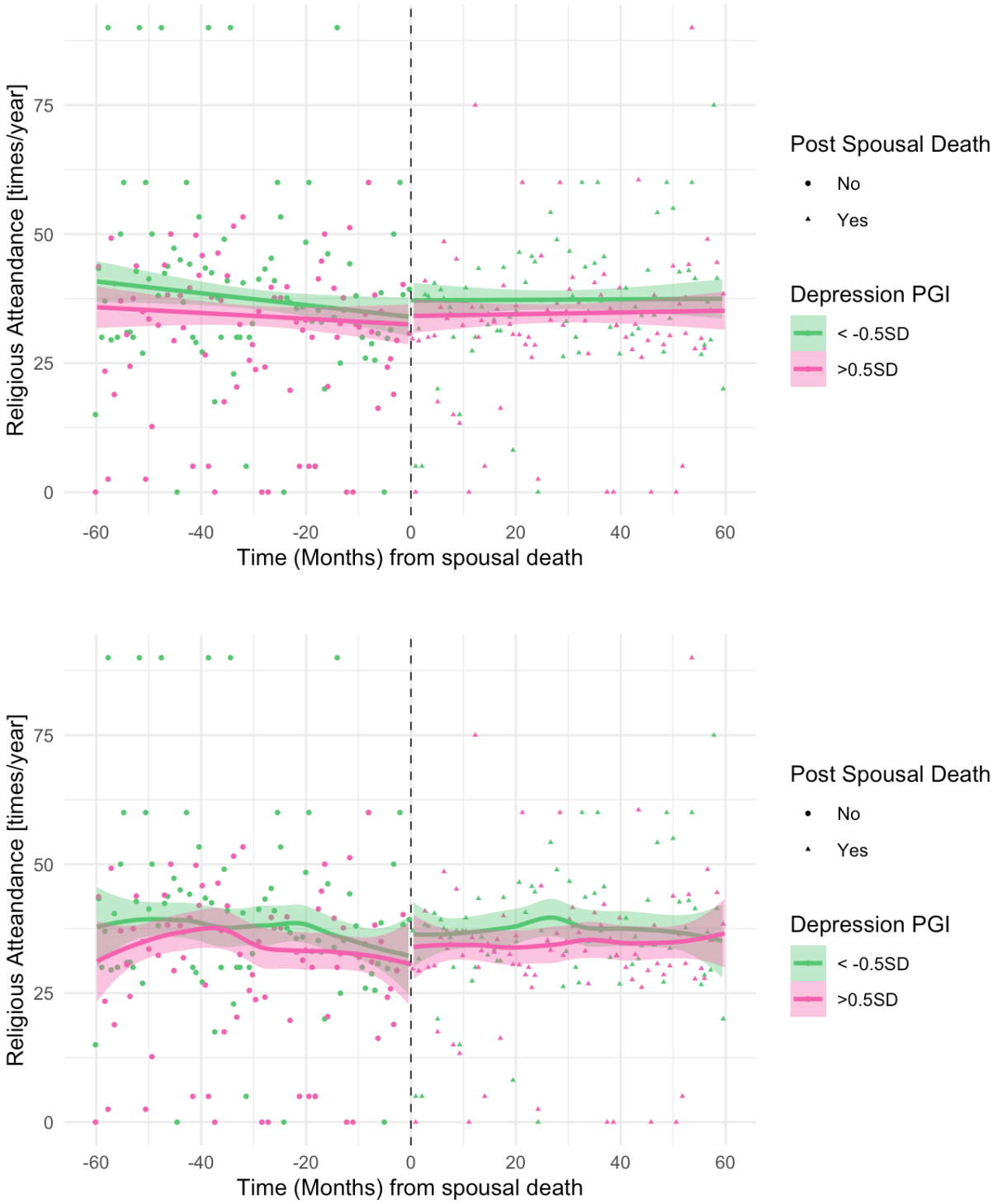
[35] Trajectories for respondents with higher religious attendance residualized on religious attendance PGI are graphed in orange (more than 0.5 SD above the mean, N=566, obs = 2,533), while those with less frequent religious attendance are graphed in blue (more than 0.5 SD below the mean, N=634, obs = 2,811).

Figure B.5 Trajectories of religious attendance for HRS respondents with a high religious attendance (REL) PGI and a low REL PGI - (local linear regression) [36]



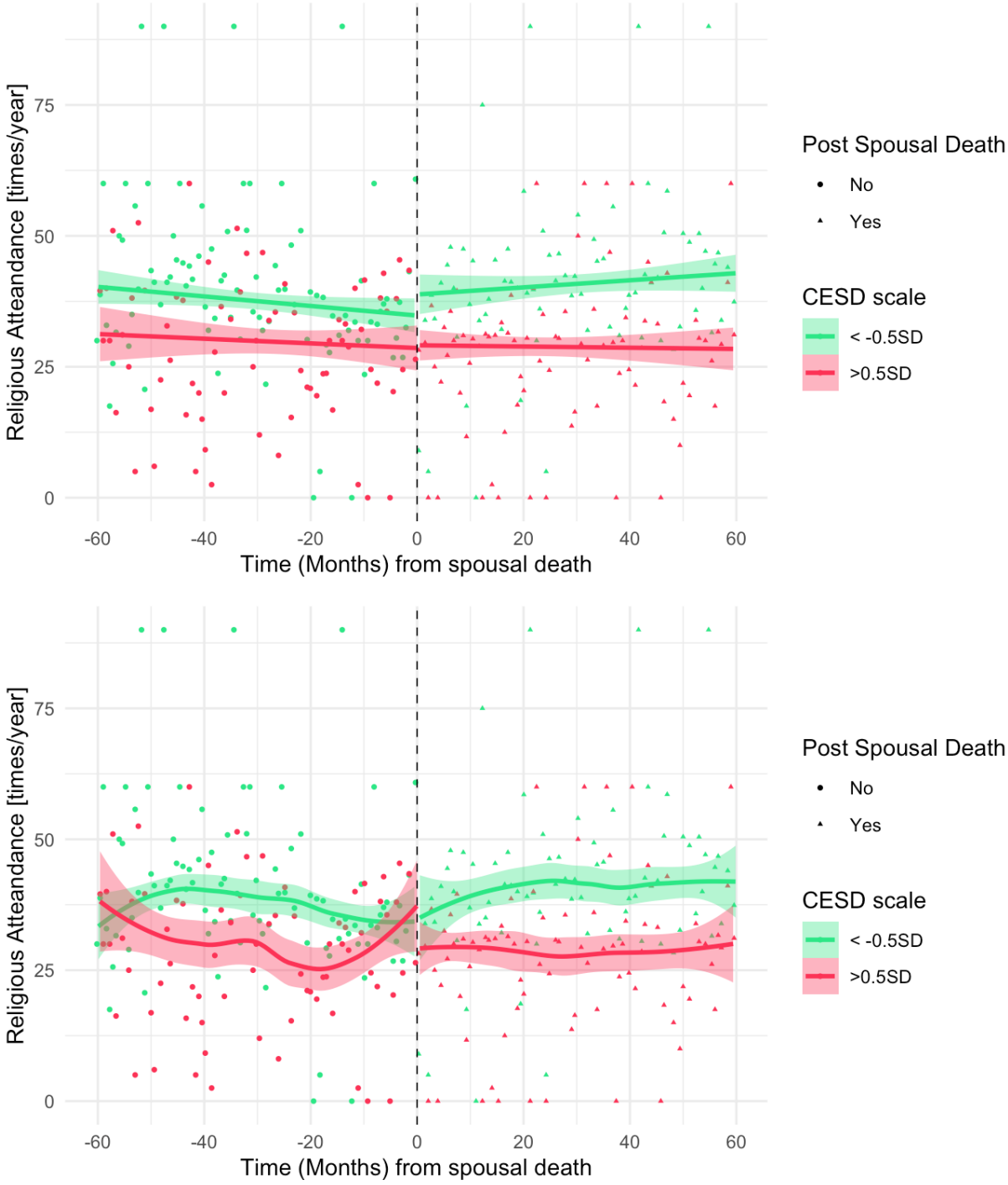
[36]Trajectories for respondents with a high religiosity PGI are graphed in red (more than 0.5 standard deviations above the mean, N=749, obs = 2,533), while those with a low PGI are graphed in green (more than 0.5 standard deviations below the mean, N=751, obs = 2,501).

Figure B.6.a & B.6.b Trajectories of religious attendance for HRS respondents with a high depression PGI and a low depression PGI - (local linear regression & local polynomial regression) [37]



[37] Trajectories for respondents with a high depression PGI are graphed in red (more than 0.5 standard deviations above the mean, N=773, obs = 2,548), while those with a low PGI are graphed in green (more than 0.5 standard deviations below the mean, N=764, obs = 2,517).

Figure B.7.a & B.7.b Trajectories of religious attendance for HRS respondents with a high CESD score and a low CESD score - (local linear regression & local polynomial regression) [38]



[38]Trajectories for respondents with a high CESD scale are graphed in red (more than 0.5 standard deviations above the mean, N=1,116, obs = 2,016), while those with a low CESD scale are graphed in green (more than 0.5 standard deviations below the mean, N=1,550, obs = 3,235).

Table B.8 Nonlinear least squares regression models predicting depressive symptoms (8-item CESD score) after spousal death among non-Hispanic whites

	CESD~DEP_PGI NLS Model1	Model2	Model3
Intercept	5.176***	4.787***	4.708***
	(0.458)	(0.460)	(0.461)
age	−0.023***	−0.024***	−0.023***
	(0.005)	(0.005)	(0.005)
gender	−0.088	−0.095	−0.099
	(0.114)	(0.112)	(0.111)
edyears	−0.086***	−0.093***	−0.090***
	(0.020)	(0.020)	(0.020)
b1	0.149**		0.116
	(0.050)		(0.088)
b2		1.977***	2.018***
		(0.194)	(0.200)
lambda		7.074***	6.875***
		(1.707)	(1.678)
b3			0.399*
			(0.203)
gamma			−1.238
			(0.957)
Num.Obs.	2030	2030	2030
AIC	9079.5	8982.8	8975.6
BIC	9113.2	9022.1	9031.8
Log.Lik.	−4533.762	−4484.398	−4477.821
isConv	TRUE	TRUE	TRUE
finTol	0.000	0.000	0.000

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Notes:

Depressive symptoms = $\alpha + \beta_1 PGI + (\beta_2 + \beta_3 PGI) exp[-t/(\lambda + \gamma PGI)] + \beta_4 X + \varepsilon$,

Model 1 restricts the values of β_2 and β_3 to be zero, resulting in a standard linear model. Model 2 restricts values of β_1 , β_3, and γ to zero to estimate the main effect of the death of a spouse without regard to genotypes.

Table B.9 Nonlinear least squares regression models predicting depressive symptoms (8-item CESD score) after spousal death among non-Hispanic whites

	CESD~REL_PGI NLS Model1	Model2	Model3
Intercept	5.190***	4.787***	4.702***
	(0.458)	(0.460)	(0.461)
age	−0.023***	−0.024***	−0.024***
	(0.005)	(0.005)	(0.005)
gender	−0.096	−0.095	−0.098
	(0.114)	(0.112)	(0.112)
edyears	−0.084***	−0.093***	−0.088***
	(0.020)	(0.020)	(0.020)
b1	−0.132**		0.048
	(0.051)		(0.114)
b2		1.977***	1.997***
		(0.194)	(0.201)
lambda		7.074***	6.911***
		(1.707)	(1.657)
b3			−0.275
			(0.206)
gamma			−1.391
			(1.548)
Num.Obs.	2030	2030	2030
AIC	9081.6	8982.8	8978.7
BIC	9115.3	9022.1	9034.9
Log.Lik.	−4534.805	−4484.398	−4479.352
isConv	TRUE	TRUE	TRUE
finTol	0.000	0.000	0.000

+ p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Notes:

Depressive symptoms = $\alpha + \beta_1 PGI + (\beta_2 + \beta_3 PGI) exp[-t/(\lambda + \gamma PGI)] + \beta_4 X + \varepsilon$,

Model 1 restricts the values of β_2 and β_3 to be zero, resulting in a standard linear model. Model 2 restricts values of β_1 , β_3, and γ to zero to estimate the main effect of the death of a spouse without regard to genotypes.

Conclusion

This dissertation contributes valuable insights into the genetic architecture of religious attendance and its associations with demographic traits. The key findings from the three chapters are as follows:

Chapter 1 finds over 300 significant genetic correlations, with religious attendance negatively associated with high-risk health behaviors and positively correlated with better physical and mental health. The PGI construction method is robust and predicts religious attendance in various populations, with the marginal R2 of PGI predictions in three American longitudinal surveys being around 1%, which is non-trivial compared to predictors like age and sex. The unique nature of religious attendance is highlighted through the two-common factor model and GWAS-by-subtraction analyses, emphasizing the importance of genetic data integration in understanding genetic factors contributing to religious attendance and its associations with social and demographic traits. Genomic SEM mediation analysis reveals the positive direct genetic effect of religious attendance on the number of children, mediated by education and less risky sexual behavior. A possible molecular mechanism for shared genetic architecture between religious attendance and health is suggested through cell immunity, with three genes (CD47, HHLA2, and TENM2) playing a distinctive role in religious attendance that cannot

be explained by the types of social interaction measured by going to sports clubs/gyms or pubs/social clubs.

Chapter 2 reveals a consistent positive phenotypic correlation in religious assortative mating among spousal pairs of older Americans across birth cohorts, despite the decline in religious attendance. However, there is limited evidence of significant religious assortative mating at the genotypic level. We found a significant positive phenotypic correlation between religious attendance and fertility, but genetic correlations showed varied results. No direct or indirect genetic effects of religious attendance on age at first birth or the number of everborn children were found, but direct genetic effects of religious attendance on education were identified. Further research is needed for the sibling model, as a negative indirect sibling effect on religious attendance was found for respondents from the Wisconsin Longitudinal Study. The potential confounding biases from population structure, assortative mating, and genetic nurture warrant caution in interpreting results, emphasizing the need for family-based designs, more diverse samples, and comprehensive genetic information in future studies.

Chapter 3 highlights the different impacts of two adverse events, with the spike in depressive symptoms being more significant and dramatic for those personally experiencing the loss of a loved one. Religious attendance also changes after adverse events, as respondents from the National Longitudinal Study of Adolescent to Adult Health with high religious attendance

PGI substantially increased their attendance for religious activities following 9/11. High religious attendance PGI and low depression PGI appear to be protective against depression, suggesting that religiosity has both direct and buffering effects on mental health. Religious attendance may act as a buffer for adverse life events and affect individuals differently based on their genetic endowments. Therefore, research on mental health should consider the role of religiosity and genetic factors in order to better understand the complex interplay between these variables and their impact on mental health outcomes.

In this dissertation, we contribute to the relatively unexplored area of the role of genetics in religious attendance and its relationship with demographic and social traits. We find that genetic effects on religious attendance, although small, are statistically significant. By identifying strong genetic correlations between religious attendance and other social traits, our research sheds light on potential confounding factors in causal studies. The use of Genomic SEM emphasizes the intricate nature of these relationships, offering insight into the complexity of the underlying structure. One key finding is the consistent phenotypic similarity of religious attendance between spouses over time, despite increasing trends of interfaith marriages. In contrast, the genotypic similarity of religious attendance appears to be negligible. Our research also shows that direct genetic effects of religious attendance on fertility are not observed in Health and Retirement Study data, suggesting that the influence of religious attendance on fertility is mediated by education. We also note the potential role

of religion in easing grief after the death of a spouse. Participation in religious activities or other forms of social support might act as a protective factor against adverse life events that can lead to depressive symptoms. Additionally, the influence of religious participation may differ among individuals with distinct genetic predispositions. For those with a higher religious attendance PGI, engaging in religious activities could serve as a more successful coping mechanism when faced with stressful life events.

However, we acknowledge the limitations of using only non-Hispanic whites and religious attendance as the measurement of religiosity, which may not capture the full spectrum of religious experiences and beliefs. The implications of this dissertation extend beyond our current findings, as it underscores the importance of examining gene-environment effects with diverse populations and different environmental changes to better understand the complex interplay between genetics and religiosity. In addition, future research on the gene-environment interplay in psychiatry should consider religiosity both for explanatory and therapeutic purposes. Furthermore, our research advocates for the integration of genetic data in social science, the use of within-family designs, and increasing the sample size of genotyped closely related individuals. This approach will facilitate a more comprehensive understanding of direct genetic effects and gene-environment interplay, opening up new avenues for more targeted and informed investigations in the future.

A Primer on Statistical Genetics

This primer serves to provide an overview of statistical genetics for social scientists who possess basic statistical knowledge but lack familiarity with genetics or molecular biology, thus aiding their understanding of the methods utilized in this dissertation. The study of behavioral genetics has yielded a wealth of empirical evidence over the years, resulting in the proposal of three laws by Turkheimer (2000) based on the findings derived mostly from kinship-based studies. Fifteen years later, a meta-analysis of the heritability of human traits based on fifty years of twin studies (Polderman et al., 2015) still supported these three laws:

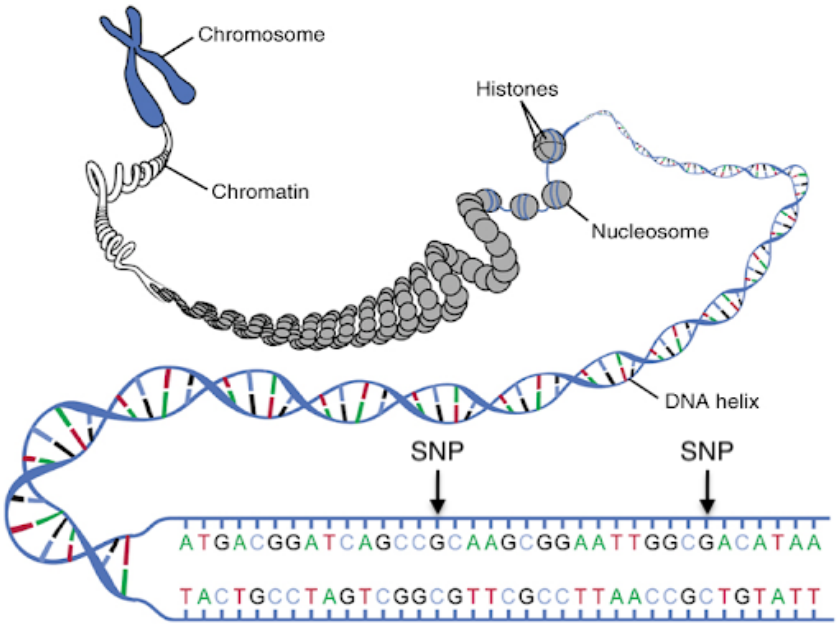
- First Law - "All human behavioral traits are heritable."
- Second Law - "The effect of being raised in the same family is smaller than the effect of genes."
- Third Law - "A substantial portion of the variation in complex human behavioral traits is not accounted for by the effects of genes or families."

Based on the three laws of behavioral genetics, researchers began using molecular genetic methods to identify specific genes that contribute to complex human traits. One such method is genome-wide association studies (GWAS), which allows researchers to identify common genetic variations associated with a particular trait or disease. Before delving into the details of GWAS, it is important to understand the basic structure of DNA and how it relates to genetic variation.

As Figure 1 [adapted from Figure 3.22 (J. Gordon Betts et al., 2016)] shows, the chromosome is the condensed form of chromatin, which is composed of DNA and associated proteins (Griffiths et al., 2005). Along the chromatin strand, DNA is wrapped around a series of histone proteins. A nucleosome is a single encapsulated DNA-histone complex.

Deoxyribonucleic acid (DNA for short) is a molecule that carries genetic information about the development and function of an organism. The shape of DNA is known as a double helix, as shown in Figure 1. Each strand has a backbone of alternating sugar (deoxyribose) and phosphate groups. Attached to each sugar is one of four bases: adenine (A), cytosine (C), guanine (G), or thymine (T). The two strands are connected by chemical bonds between the bases: adenine (A) bonds with thymine (T), and cytosine(C) bonds with guanine (G). The sequence of the bases along DNA's backbone encodes biological information, such as the instructions for making a protein or RNA molecule.

Figure 1 DNA Macrostructure (J. Gordon Betts et al., 2016)

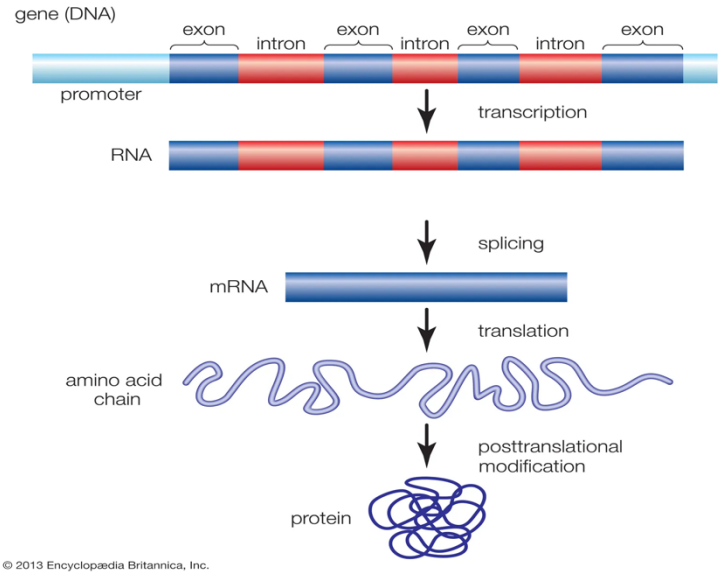


SNPs are short for Single Nucleotide Polymorphisms and are frequently called SNPs (pronounced “snips”) (Collins et al., 1999). SNPs are the simplest and the most common form of DNA variation among individuals. Each SNP represents a difference in a single DNA building block called a nucleotide. For example, a SNP may replace the nucleotide guanine (G) with the nucleotide thymine (T) in a certain stretch of DNA. These simple changes occur throughout the genome at a frequency of about one in 1,000 bp (base pairs), which is a fundamental unit of DNA. SNPs could be responsible for the diversity among individuals, genome evolution, and the most common human traits such as drug response, susceptibility to environmental factors, and complex diseases.

Humans have 23 pairs of chromosomes and approximately 20,000 protein-coding genes (Griffiths et al., 2005). Genes are the basic units of inheritance. This dissertation only focuses on protein-coding genes that code for specific proteins, or segments of proteins, which have different functions within the body. Most protein-coding genes in the human genome consist of exons and introns, as Figure 2 shows. The messenger RNA (mRNA) coding sequences called exons are separated by non-coding sequences called introns. In many genes, the introns are much longer than the exons. Introns may contain sequences that regulate how genes are expressed or transcribed and how mRNA is processed. When genes are transcribed, those exons and introns are included in the initial products. However, introns are removed during

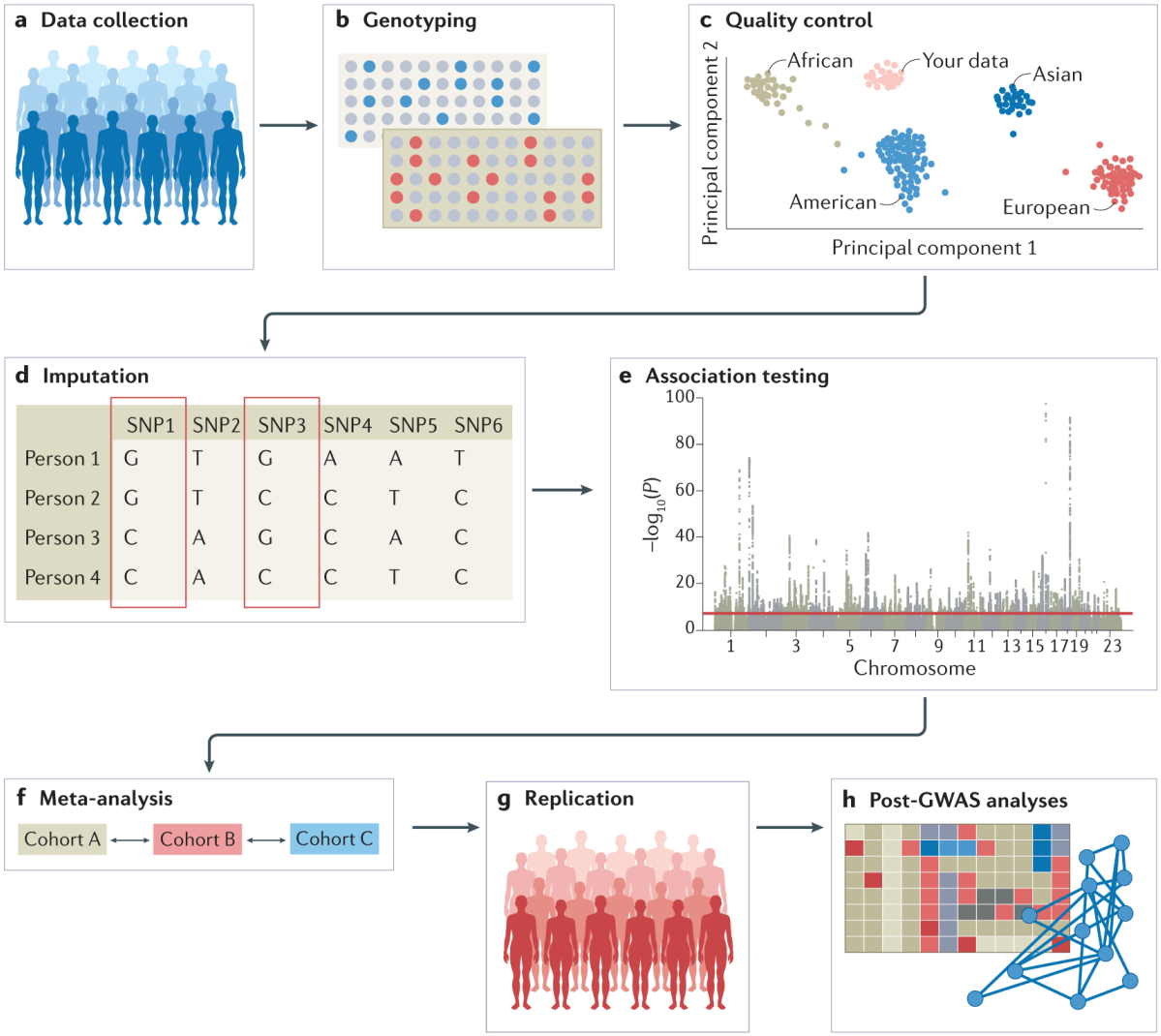
the process called splicing, so only exons are included in the mature mRNA and used to dictate what proteins are produced. Pleiotropy occurs when one gene influences two or more seemingly unrelated phenotypic traits. Once one gene encodes an essential protein used for important activities inside of the organism, the gene is likely to influence many different phenotypic traits.

Figure 2. The structure of a gene (*Encyclopædia Britannica*, 2013)



Genome-wide association studies (GWAS) test millions of genetic variants across many genomes to find those statistically associated with a specific trait or disease (Uffelmann et al., 2021). In other words, GWAS seek to identify the SNPs that are common to the human genome and to determine how these polymorphisms are distributed across different populations.

Figure 3. Genome-Wide Association Studies (GWAS) Process(Uffelmann et al., 2021)



The typical steps for conducting a GWAS are shown here - first, genotypic data are collected from a study cohort using microarrays to capture common variants or next-generation sequencing methods for whole-genome sequencing (WGS) (Uffelmann et al., 2021). Quality control includes steps like deletion of bad SNPs and detection of population stratification in the sample, and calculation of principal components. Then we can use information from matched reference populations (from repositories such as the 1000 Genomes Project) to impute untyped SNPs. The next step is to run genetic association tests on the phenotypic

traits of interest for each SNP using an appropriate model (for example, additive, non-additive, linear, or logistic regression) by adjusting common confounders, including population stratification. Output is inspected for unusual patterns, and summary statistics are generated. GWAS requires enormous sample sizes because of multiple testing, so many meta-analyses combine results from multiple smaller cohorts using standardized statistical pipelines. The SNP heritability is defined as the fraction of the phenotypic variance explained by additive effects of a given set of genetic variants. We can calculate SNP heritability after conducting GWAS.

Population stratification refers to the differences in the frequencies of genetic variants between individuals from different ancestral populations (Cardon & Palmer, 2003). If a genetic study includes individuals from different populations, it may lead to spurious associations between genetic variants and traits, which are not related to the trait but are simply due to differences in ancestry. Uncontrolled population stratification can lead to false discoveries, as shown by the example of the chopstick gene in Figure 4 (Hamer & Sirota, 2000). An association between a genetic variant and chopstick use was found, but further investigation revealed that the association was not due to the gene's function but rather to differences in ancestry between study groups. Therefore, controlling for population

stratification is crucial in genetic studies to avoid incorrect conclusions about the genetic basis of a trait or disease.

Principal Component Analysis (PCA) is a widely used method to control for population stratification in genetic studies(Price et al., 2010). It involves calculating the principal components from a set of genetic variants and using them as covariates in statistical models. In GWAS, typically 10-20 principal components are included in the analysis to adjust for population stratification. By including these principal components in the model, the effects of ancestry on the trait of interest can be controlled, reducing the risk of false associations.

Figure 4. Chopstick gene example of population stratification (Abdellaoui, 2020)

Population stratification: chopstick example

Sample 1 Americans: $\chi^2=0$, $p=1$			
	Use of chopsticks		
	Yes	No	Total
Allele 1	320	320	640
Allele 2	80	80	160
Total	400	400	800

Sample 2 Chinese: $\chi^2=0$, $p=1$			
	Use of chopsticks		
	Yes	No	Total
Allele 1	320	20	340
Allele 2	320	20	340
Total	640	40	680



Sample 1 + 2 = Americans + Chinese: $\chi^2=34.2$, $p=4.9 \times 10^{-9}$			
	Use of chopsticks		
	Yes	No	Total
Allele 1	640	340	980
Allele 2	400	100	500
Total	1040	440	1480

Linkage Disequilibrium (LD) score regression

Linkage disequilibrium (LD) is the nonrandom association of alleles of different loci (Bush & Moore, 2012). As the left of Figure 5 shows, within a family, linkage occurs when two genetic markers (points on a chromosome) remain linked on a chromosome rather than being broken apart by recombination events during meiosis, shown as red lines. In a population, contiguous stretches of founder chromosomes from the initial generation are sequentially reduced in size by recombination events. Over time, a pair of markers or points on a chromosome in the population move from linkage disequilibrium to linkage equilibrium, as recombination events eventually occur between every possible point on the chromosome.

Figure 5. Linkage Disequilibrium (Bush & Moore, 2012)

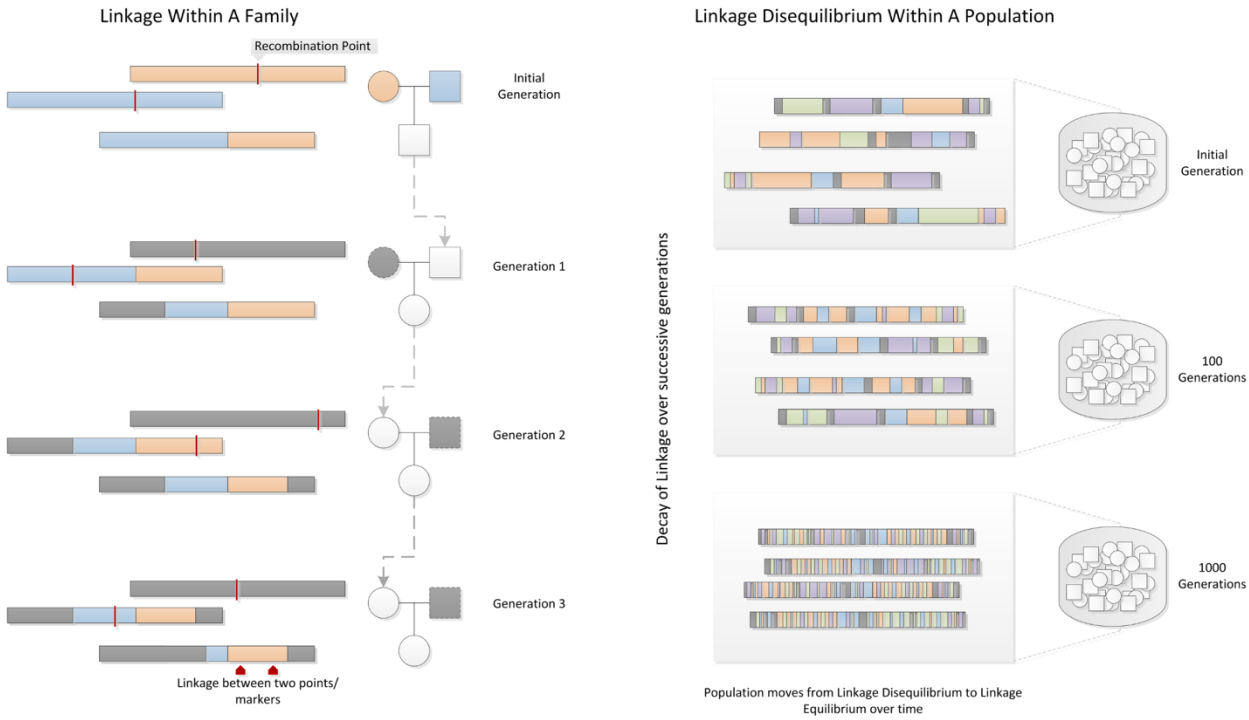
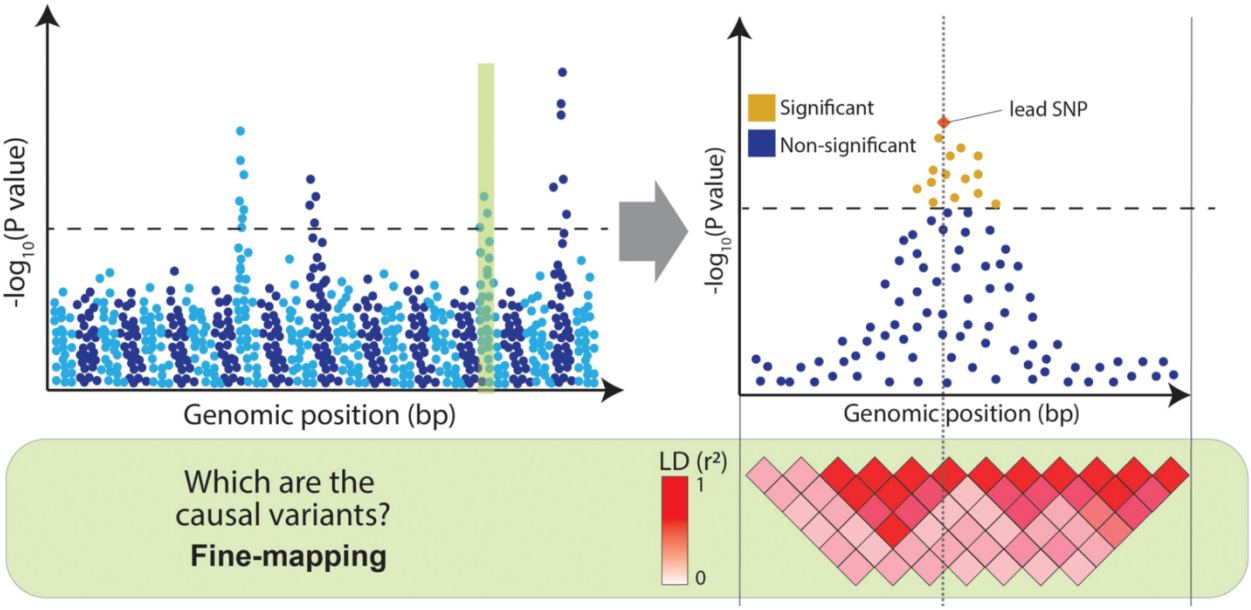


Figure 6. Interpreting GWAS (Cano-Gamez & Trynka, 2020)



LD poses challenges in interpreting GWAS results. Figure 6 shows a Manhattan plot that represents the association between genetic variants and a trait at a genome-wide level (left

panel). Variants above the dotted line are considered genome-wide significant associations. However, when focusing on a specific locus (right panel), an island or tower shape of SNPs with high significance is often observed, which is caused by indirect association within the LD structure. The panel below demonstrates the high LD between SNPs (shown in shades of red), which makes it challenging to identify the causal SNP because of the correlation between the trait and other SNPs due to LD.

To better understand the patterns of LD in the genome, Figure 7A provides a simplified visualization of the LD structure. Each dark blue square represents a SNP, while the light blue squares depict the correlations between adjacent SNPs that result from LD. By summarizing these LD patterns into a score, we can assess how strongly a given SNP is correlated with the surrounding SNPs. Specifically, for each SNP, we add up the LD across all of its neighbors to obtain a score that reflects its degree of correlation with nearby SNPs.

Consider a genetic effect originating from the causal SNP represented by the black square in Figure 7A. Among the SNPs in the vicinity, none possess any effect except for the causal SNP with a small but significant effect. Upon estimation of the beta coefficients in a GWAS, as depicted in Figure 7B, all SNPs in LD with the causal SNP display non-zero beta coefficients. The extent of LD is a challenging aspect to quantify, and there is no definitive

statistic to measure it. The LD score was developed to counterbalance the inflated test statistics resulting from GWAS analyses.

LD score regression equation:

$$E(\chi^2 | l_j) = \frac{h^2 N}{M} l_j + Na + 1$$

Consider the consequences of genome-wide testing using a regression model with a trait for every SNP. The test statistics will be inflated for SNPs with greater LD, measured by a higher LD score l_j. For a polygenic model, the expected χ2 statistic of genetic variant j is given by the equation provided, where N represents the sample size, M represents the number of SNPs, Na accounts for confounding biases such as cryptic relatedness and population stratification, and l_j is the LD score of variant j (which measures the amount of genetic variation tagged by j). This relationship holds for meta-analyses. By regressing the χ2 statistics from GWAS against LD scores (LD Score regression), we can estimate the slope and the intercept. The intercept minus one provides an estimate of the mean contribution of confounding bias to the inflation in test statistics. Using the slope and adjusting for sample size, we can obtain the average heritability ($\frac{h^2}{m}$) explained per SNP.

Figure 7A Actual genetic effects

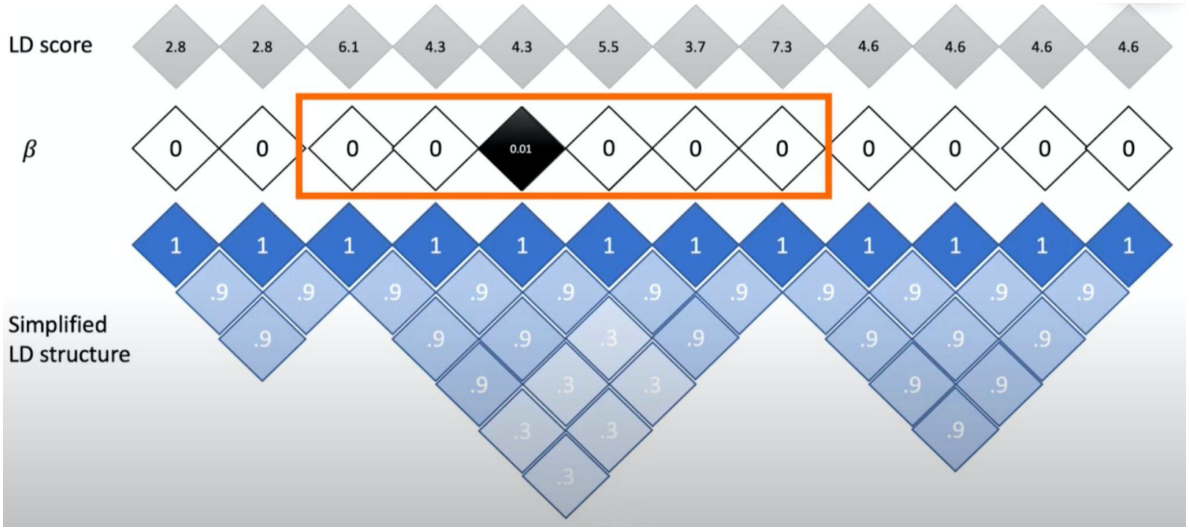
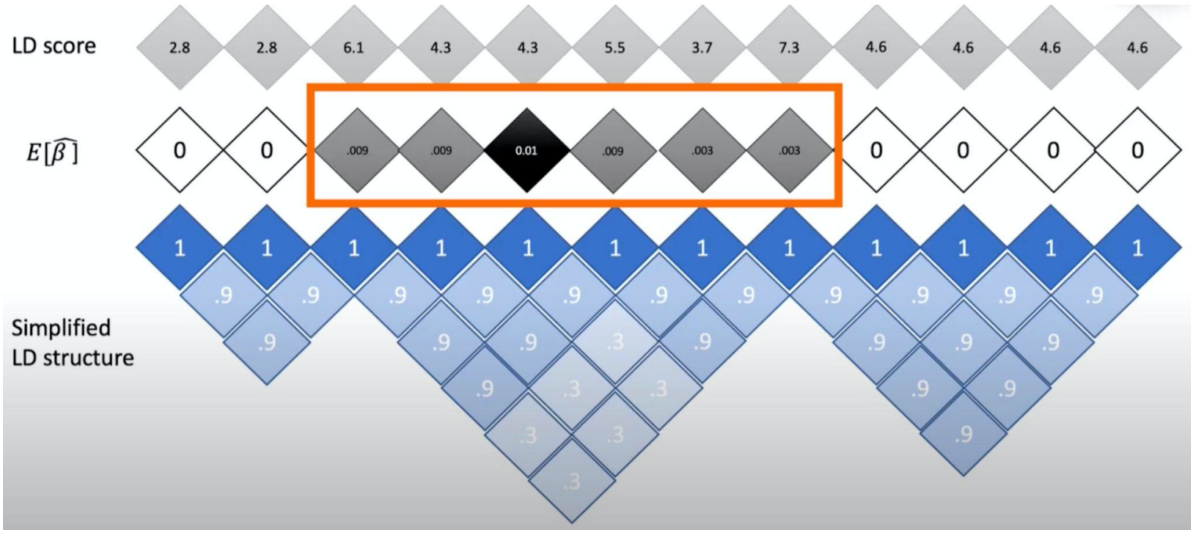


Figure 7B GWAS results regarding LD structures



LD score regression can also be used to estimate the genetic covariance of two traits from the product of their Z scores, which quantify how far a particular observation deviates from the average (mean) of a dataset, measured in terms of standard deviations. This approach is robust to sample overlaps in GWAS. The overall genetic correlation (rG) reflects the proportion of variance that two traits share due to genetic causes or the degree of pleiotropy

or genetic causal overlap. A genetic correlation of 0 indicates that the genetic effects on one trait are independent of the other, while a correlation of 1 implies that all of the genetic influences on the two traits are identical.

Genomic Structural Equation Modelling (SEM) (Grotzinger et al., 2019)

Structural Equation Modeling (SEM) is a versatile modeling framework that integrates various multivariate techniques. It combines measurement theory, factor analysis, path analysis, regression, and simultaneous equations into a dynamic framework that continues to develop with the integration of new statistical tools and techniques (Ullman & Bentler, 2012). SEM is particularly useful for complex social constructs that are measured with error, such as religiosity, as well as research questions that focus on indirect effects, mediated relationships, and complex, multi-faceted constructs that require systems-level analyses, such as genomic architecture.

In SEM, a variable can serve as both a predictor and an outcome, allowing for a deeper understanding of indirect effects. Rather than analyzing raw data, SEM involves analyzing the variance/covariance matrix of observed variables, such as summary statistics from GWAS. The aim is to simplify this matrix by specifying an underlying structure, resulting in an implied variance/covariance matrix that can be compared with the observed matrix. Model

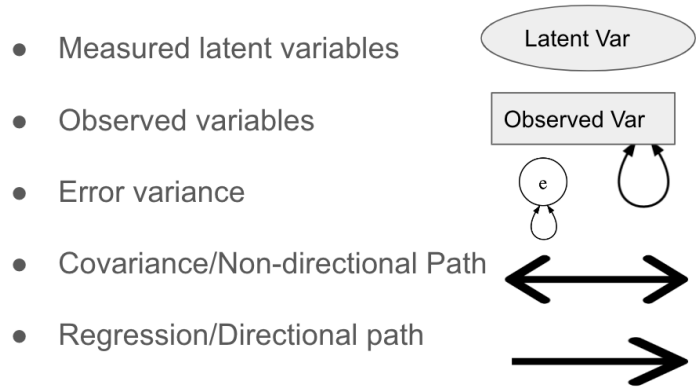
identification is important in SEM, and parameters must be fixed or constrained to ensure a valid and interpretable model. Overall, SEM is a valuable tool for understanding complex systems of relationships among variables.

A Genomic SEM applies the SEM framework to GWAS summary statistics data (Grotzinger et al., 2019). The steps of a Genomic SEM include -

- Stage 1: Establish a measurement model using latent variables - using a multivariable extension of LD score regression to estimate an empirical genetic covariance matrix (S)
- Stage 2: Fit regression paths [structural equations] between concepts - these paths are represented by parameters (θ) that may be fixed or freely estimated by minimizing the discrepancy between two matrices
- Test hypotheses on model parameters
- Assess model fit - the divergence between the model-implied covariance matrix $\Sigma(\theta)$ and the empirical covariance matrix (S)
- Use multiple evaluation metrics - SRMR (standardized root mean square residual), model χ^2, AIC (Akaike Information Criterion), CFI (Comparative Fit Index)

Path analysis is a visualization tool used in SEM that presents a theoretical model using standardized notations. In this method, an oval or ellipse denotes a measured or latent variable, while a rectangle represents an observed or manifest variable. The small circle represents the error variance of the disturbance term, as an error can also be considered as a latent variable measuring what remains. To simplify the notation, a circular cross is used near the observed variables to provide error estimates. The double-headed arrow represents a covariance path that specifies two related or correlated variables in the model, indicating a non-directional association. On the other hand, the single-headed arrow represents a directional path that need not be causal. This diagrammatic representation of the model makes SEM very visually appealing.

Figure 8. SEM Path Diagram notations



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