Changing polygenic penetrance on depression among adults in the United Kingdom: the role of historical contexts and birth cohorts

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Abstract

Changes that occur over time across different birth cohorts is a major field of research in demography and sociology, as cohort effects reflect the importance of historical changes shaping people's lives. Ongoing discussion of depression also covers this aspect of research. The prevalence of depression is believed to have a historical trend and to occur more frequently among recent birth cohorts. Observed increases in the occurrence of depression could be due to various factors, including changes in policies, macro-economic conditions, and lifestyles. Genetic influences on depression may affect individual responses to contextual aspects, leading to variation in genetic penetrance on depression across birth cohorts (known as gene-by-cohort interactions). Accordingly, this paper investigates whether polygenic prediction of depression varies by birth cohorts in the UK. Through theoretical considerations of gene-environment interactions, I perform a regression analysis using the UKHLS genetic sample. I show some evidence supporting gene-by-cohort interactions in depression among adults in the UK, which I further link with exposures to economic recessions.

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1 Introduction

Mental health is a global health concern. Social media, newspapers, official reports, researchers, politicians, and others emphasise the importance of a deeper understanding of mental health disorders. Given the alarming statistics, this attention is unsurprising: mental disorder is the main cause of disability worldwide (Lozano et al., 2012) and one of the main causes of overall sickness (Vos et al., 2015).

Depression is one of the most common mental health disorders. The frequency of depression occurrence ranges from 8% to 12% in different countries (Flint and Kendler, 2014). The severity of depression varies from mild symptoms to major depression. All of these factors contribute to growing research covering different aspects of depression. There are various causes of depression and social scientists refer to many different factors, including historical exposures. Depression is also heritable and there is an interdisciplinary field investigating how various environmental aspects interplay with genes.

Accordingly, depression can be triggered by socio-economic factors, such as educational attainment (Lee, 2011), job loss (Drydakis, 2015; Paul and Moser, 2009), and recessions (Frasquilho et al., 2015; Jahoda, 1988). More broadly, the prevalence of depression is believed to have a historical trend and to occur more frequently among recent birth cohorts (Marcus and Olfson, 2010; Bell, 2014). Observed increases in depression occurrence could be due to various factors, including environmental and lifestyle changes, policy contexts, and economic downturns. Genetic influences on depression may also affect individual responses to contextual components (for example, by shaping stress-internalisation processes). The latter would lead to variation in the genetic penetrance on depression across birth cohorts. As previously suggested, estimates of the percentage of variation in social outcomes explained by genetic and environmental differences are likely to be context specific, varying systematically across different social conditions, policy environments, or subgroups of the population (Boardman et al., 2011). These notions have yielded a growing field of research wherein birth cohorts are potential modifiers of genetic influences.

This paper identifies changes in the polygenic penetrance on depression within the UK during the 20th century. The research investigates whether the polygenic prediction of depression varies by birth cohorts in the UK or, in other words, whether we observe gene-by-cohort interactions for this mental health trait. I also aim to answer the question of whether historical contexts (such as economic recessions) contribute to gene-by-cohort variations.

In a conventional demographic classification for the UK, there are six birth cohorts. Two cohorts are devoted to people exposed to the two World Wars: a WWI cohort born between 1916 and 1930; and a WWII cohort with birth years in 1931–1945. A demographic cohort

of those born in 1946–1964 is distinguished as Boomers to reflect the period of the Baby Boom. After that, there is a Generation X cohort (people born in 1965–1980) followed by Millennials or Generation Y (those born between 1981 and 1995). People born at the very end of the century are referred to as Generation Z.

The focus on gene-by-cohort interactions has the potential to shed a light on how historical contexts shape polygenic prediction across different generations. The insight for social science, in particular, is whether the rise in the prevalence of depression at certain historical points in the 20th century is driven by those with a higher polygenic risk of depression; alternatively, prevalence could be independent of genetic risks. Within the literature, there is a notable gap in studies covering the UK context. Consequently, this paper contributes to existing knowledge by providing a gene-cohort interaction analysis of depression in the UK.

In this study, I use data from the Understanding Society genetic sample to investigate how associations between depressive symptoms and the polygenic risk score for depression differ across successive birth cohorts in a national sample of UK adults. I start my investigation by presenting the theoretical background for the issue. First, I discuss findings on the increasing prevalence of depression in the UK. Then, I demonstrate genetic factors related to the development of depression. Afterwards, I provide an overview of gene-by-cohort interaction studies where I also discuss the role of policy changes that could potentially shape heritability variations. In the sections thereafter, I explain my empirical strategy by describing measures and statistical methods. I discuss the results extensively and assess possible biases.

Next, I perform a robustness analyses that initially takes mortality selection into account. Selection into genotyping results in differential mortality curves among genotyped and non-genotyped participants in the UKHLS survey (Akimova, 2020). This is known to be a source of potential bias in gene-cohort analysis (Domingue et al., 2017). Hence, I perform a weighted analysis to obtain estimates that are less biased by mortality selection. Finally, I check the robustness of my results through analysis of overlapping, age-comparable sub-samples of birth cohorts. Aging trends and cohort trajectories are inherently connected, and some age groups are omitted from some cohorts in the UKHLS dataset. Replication thus advances the understanding of observed results.

2 Background

2.1 Cohort trends in depression in the UK

Cohort trends are a major area of study in demography and sociology (Ryder, 1965). This particular interest is linked to the notion that cohort effects indicate the importance of historical changes that potentially shape people's experiences at least to some extent. To reveal and to understand the links between macro conditions and individual-level outcomes is the traditional focus of sociology.

The first serious discussions of an increase in the prevalence of mental health problems occurred during the 1970s (Marcus and Olfson, 2010). Bell (2014) found some support for this proposition in the UK context; through the use of BHPS, the study claims more recent cohorts have poorer mental health. In contradiction to Bell (2014), a study by Spiers et al. (2011) indicates no clear evidence of an upward linear trend in mental health problems across birth cohorts in the UK. However, some evidence suggests that a spike in depression occurred among people born in the middle of the 20th century, i.e. the cohort of Baby Boomers (Spiers et al., 2012; Rice et al., 2010). Based on the National Psychiatric Morbidity Surveys, Spiers et al. (2012) show that the prevalence of depression is higher among men born between 1950 and 1956 than in the earlier cohort of those born between 1943 and 1949. Notably, trends among women showed less consistency. Researchers found some significant upward and downward trends among earlier cohorts with rates stabilising after 1963 as a birth year (Spiers et al., 2012, p. 2051). To measure depression, researchers used a fully structured diagnostic instrument (the Clinical Interview Schedule-Revised, or CIS-R).

In the most recent cohort studies, the focus shifted to cohort-specific hypotheses. Thomson and Katikireddi (2018) investigated cohort variations in depression, for example, by paying particular attention to the so-called 'Jilted' generation (those born in the UK after the year 1979, or Millennials in conventional terms). The study involved repeat cross-sectional data obtained from the Health Survey for England for the period between 1991 and 2014. The researchers based their investigation on the GHQ depressive symptoms score that I apply in my analysis as well. Thomson and Katikireddi (2018) hypothesised that high material disadvantages caused by social and economic policies in the UK would lead to a higher prevalence of symptoms of depression (among others) in Millennials. But the researchers found no evidence to support this hypothetical claim. Moreover, there is limited insight into overall trends since the vast majority of associations are not significant and bounded around 0% changes (Thomson and Katikireddi, 2018, p. 137).

In terms of research trends for the latest cohorts, it is important to note that recent years have seen a growing volume of literature on the mental health problems of teenagers from

different birth cohorts (those born at the end of the 20th century and those born in the 21st). Research suggests that more recent cohorts of teenagers suffer from a greater prevalence of mental health problems than teens born before the 2000s. Such trends are found both for the UK context (Fink et al., 2015; Collishaw et al., 2010) and worldwide (Twenge et al., 2010; Hagquist, 2010). For example, Patalay and Gage (2019) identify an increase in depressive symptoms from 9% to 15% among UK teenagers born in 1991/92 (ALSPAC study) and those born in 2000/02 (MCS study) at the age of 15. Also, the prevalence of self-harm increased from 11.8% to 14.5%.

To date, there is little overall agreement on the shape of cross-cohort trends in depression in the UK. What seems to be robust across studies is a steady rise in the prevalence of mental health problems among those born prior to the 1960s. Also, there are consistent increases in depression observed among the most recent generations (those born after the 2000s). Regarding these trends, findings from the UK are consistent with those from the US. In a more detailed view, Twenge et al. (2019) show that the highest occurrence of depression and psychological distress in the US is likewise observed among the mid- and end-of-century cohorts. One plausible explanation for the similarity of trends in different contexts is the link to mechanisms that exist in both countries.

However, the literature on *explanans* linking birth cohorts and mental health is rather limited. This poses additional puzzles. Why do we observe some differences among UK cohorts across the 20th century? In the narrative for the UK context over the last century, there has been a wide range of historical and economic upturns and downturns that includes shifts in gender roles. Any of these could have impacted generational well-being in one way or another. Child labour was a common trend among people born at the beginning of the century, for instance, while female occupational employment was limited. A period of major recession and low growth occurred prior to World War II. In contrast, the post-war period (1950s–1960s) is known as the Golden Age – a time of economic boom and full employment. From the 1970s to the 1980s, a recessive period affected labour market participation. These periods of prosperity and challenge were experienced by people from different cohorts to varying extents. For women, the 20th century is of particular importance due to noticeable changes in labour participation and social norms in general. Increases in mental health awareness, coverage of regulations, and shifts in social norms regarding depression reporting during this time period are also important. All of these could conceivably contribute to cohort differences.

The work by Thomson and Katikireddi (2018) links cohort differences with the Great Recession of 2008. They observe an association between the global recession and austerity reforms in the UK with worsening mental health. This was especially evident among the

young working generations, while gaps between earlier cohorts stayed constant. They do not give a definite answer on whether austerity measures broadened generational inequalities in mental health, however. Still, they offer an important insight: the contribution of an economic downturn that was experienced by different generations in different ways. It is known that prolonged economic recessions are associated with increased rates of depression (Stuckler et al., 2017; De Vogli, 2014). Recessions do not affect everyone equally, but rather trigger social determinants of mental health (for instance, incidents of unemployment). These social determinants are partially cohort-specific due to age differences and status of labour market participation. Consequently, recessions widen the gaps between working-age generations and retired cohorts. Direct assessment of some of the factors, such as unemployment or economic inactivity, is notably problematic due to endogeneity and self-selection; however, birth cohorts are exogenous.

To conclude, analysis of the literature shows that birth cohorts have different degrees of mental illness prevalence. There is no conclusive evidence showing this relationship follows one universal pattern. Moreover, much research into this topic is descriptive in nature and our knowledge of factors attributed to cohort differences is limited. This paper does not aim to provide a causal explanation. Instead, I offer insight into whether cohort differences in depression are associated with its changing polygenic penetrance. The next section thus discusses the genetic basis for depression and the phenomenon of gene-by-cohorts variation.

2.2 Genetic grounds for depression

The earliest stages of research noted that depression develops in families (Tsuang and Faraone, 1990). Later, twin studies showed that if a person's parents suffer from depression, their risk of developing the illness ranges from 20% to 40% (Keyes, 2005; Sullivan et al., 2000; McGue and Christensen, 2003; Jansson et al., 2004). This range is also known as the heritability estimate for depression. However, twin studies are also likely to overestimate the extent of heritability of traits and may not present the true genetic component or its size (Maher, 2008; Manolio et al., 2009).

New methods and technologies allow researchers to address the issue in a more straightforward manner as the screening of the whole genome is now possible. One widely used approach is the so-called GWAS method. The rationale behind this method is to screen all of the SNPs in the human genome and to test their association with a certain phenotype. Multiple studies are looking at depression as a phenotype (Wray et al., 2018; Okbay et al., 2016; Hek et al., 2013; Terracciano et al., 2010), with the most recent one conducted by Howard et al. (2019).

We have learned from GWAS that depression is a polygenic trait. The most recent genetic discoveries from Howard et al. (2019) identified 102 independent variants, 269 genes, and 15 gene sets associated with depression. This includes both genes and gene pathways associated with synaptic structure and neurotransmission.

It should be noted that researchers highlight the importance of certain SNPs for depression risk. In major depressive disorders (MDD), rs7647854 on chromosome 3 was found to play a significant role (Power et al., 2017). Also, rs19323608 on chromosome 17 implicates the influence of genetics on the onset of depression (Okbay et al., 2016). Such detailed analyses of SNPs and their locations is required for further investigation of the causal links because GWAS is a descriptive approach that only establishes associations.

In sum, the genetic risk of experiencing depression is one factor in its occurrence. Growing research in this field reveals the associative nature of the genes-depression link, with further understanding of the biological causal mechanisms driving this correlation. These findings show that the genes-depression link is critical to a wider understanding of depression. It is also important to distinguish causal SNPs from non-causal ones: while the former hits tend to survive in all environments, the latter are likely sensitive to environments. Thus, they are also included in analyses of gene-interaction studies. In the case of a phenotype such as depression, both groups of SNPs have been discovered.

2.3 Gene-by-cohort studies

A large portion of the literature on gene-by-cohort interactions focuses on smoking. In their twin study, for example, Boardman et al. (2010) shows that heritability estimates vary across different birth cohorts in the US. While those who were born in the 1920s, 1930s, and 1950s cohorts have strong genetic associations with smoking, cohorts of the 1940s and 1960s have considerably smaller influences. Researchers link these observations with changes in smoking policy in the US: following the passage of legislation making it illegal to smoke in public spaces, gene influences were reduced significantly. However, the first Surgeon General's Report is associated with an increase in genetic influences. This observation is further tested in Domingue et al. (2016). Researchers show that despite people being aware of the harms associated with tobacco usage, a genetic influence on smoking continues to increase in more recent cohorts. Notably, the findings indicate that those who are genetically at risk of smoking are unlikely to respond to recent policy changes aimed at discouraging people from smoking. These studies of gene-by-cohort variations in smoking are good examples of how informative research in this field could help our understanding of policy changes.

There are also gene-by-cohort studies on alcohol consumption (Virtanen et al., 2019)

and BMI (Walter et al., 2016). Both studies found heritability differences among birth cohorts wherein those born earlier in the 20th century have lower levels of gene-phenotype correlations compared to those born in recent years. Additionally, Conley et al. (2016) conducted a study that aimed at evaluating how genetic penetration has changed in US society in relation to a broad spectrum of phenotypes across different birth cohorts. The research revealed that BMI and height continue having a higher genotypic penetration over the 20th century period, while heart diseases and education declined in genotypic effects. Notably, researchers did not find significant variation in genetic associations with depression across time. However, such a puzzling finding might be partly due to the use of earlier GWAS studies for the construction of polygenic scores – the case is particularly important for depression since, as I showed earlier, previous GWAS were able to identify less than 10 significant SNPs across human genome.

Moreover, findings of increased polygenic penetrance in later birth cohorts must be interpreted with caution as they could be biased from mortality selection in genetic samples. As demonstrated in Domingue et al. (2016), those who were born earlier in the century and genotyped are likely to be survivors (85+) and a non-representative subset of the respective cohorts. Accordingly, lack of correction for mortality selection might lead to the false impression of increased genetic penetrance under the condition of genetic homogeneity in earlier cohorts due to survival. Still, gene-by-cohort interactions offer potentially useful insights for understanding historical changes and cohort variations. There is a noticeable absence of studies covering the UK context in the literature of this field.

This literature review generates three hypotheses that aim to contribute to the existing knowledge. Firstly, I hypothesise that (1) *there are significant cohort variations in the prevalence of depressive symptoms, especially among mid-century cohorts* accompanied by (2) *changing genetic penetrance of depression*. Additionally, following the literature on the impact of economic downturns on mental health of different generations, I hypothesise that (3) *historical contexts (such as economic recessions) modify gene-by-cohort variations*.

3 Data

To investigate gene-by-birth cohort trends in depression in the United Kingdom, I use a well-known and widely used longitudinal survey called the UKHLS. Built from a national multi-stage sampling design, the survey covers approximately 40,000 households in England, Scotland, Wales, and Northern Ireland (Buck and McFall, 2011). Interviews are carried out every year covering a rich set of questions related to health, socio-economic conditions, and transitions along with family trajectories. The UKHLS has been collecting DNA data since

2010, and has introduced this genetic sample as an additional restricted data source.

After the release of its genetics data, the UKHLS became a unique data source for sociogenomics researchers. The genetic sample contains around 10,000 people, all of whom are adult members of households from the main Understanding Society survey. Originally, 10,484 adult members of households were selected for genome-wide array genotyping. Genotyping was performed with the Illumina Infinium HumanCoreExome BeadChip.

One of the main advantages of this dataset is that the UKHLS genetic sample includes people of all ages and is not restricted to certain birth cohorts. This is particularly important in light of my research question. For the UK context, such a data property offers a unique opportunity as it is common for genetic samples to cover specific age groups (for example, UK BioBank includes people who are more than 40 years old).

4 Measures

4.1 Depression score

To date, various methods have been developed and introduced to measure depression. Along with information on the diagnosis of this condition, depressive symptomatic data is another valuable source usually provided by surveys. While incidents of depression and its diagnosis indicate the severity of someone's mental health, symptomatic data makes it possible to look at the issue across a broader spectrum and to model the risk of developing depression. Importantly, I do not use depression diagnosis as my main phenotypic variable since it was shown that symptomatic data on mental health is more accurate and has greater validity and reliability in the context of population-based surveys (Mandemakers, 2011).

Depressive symptoms scores are available from multiple surveys and have been used in many empirical studies. The Understanding Society has two scores: GHQ and SF-12. Both of these scores follow a traditional way. Each is assessed by measuring individual psychological states through item-based questionnaires using Likert scales. I use the GHQ score for the main body of my analysis, as it is one of the most widely used and consistently observed during the full survey period. The SF-12 score was included in questionnaires later, consistently present only after 2009.

GHQ was developed as a tool to screen non-psychotic mental health problems (Goldberg et al., 1972). The modelled symptoms primarily cover depression and anxiety disorders. The overall score is a constructed sum of 12 indicators (usefulness, decision-making, unhappiness, confidence, self-worth, the ability to face problems, joy in day-to-day activities, concentration, loss of sleep, overcoming difficulties, and being under strain). Each item in the GHQ

Table 1: Descriptive statistics of UKHLS analytical sample, by birth cohorts

	All 1919-95		World Wars 1919-45		Boomers 1946-64		GenX 1965-80		Millennials 1981-95		Range
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
GHQ scale	10.99	5.26	10.32	4.60	11.32	5.49	11.18	5.36	10.95	5.73	0-36
PGScore	-.00	1.00	-.05	1.02	-.00	.98	.02	1.00	.11	.99	-3.6-3.9
Female	.56	.50	.53	.50	.56	.50	.59	.49	.57	.50	0-1
Age	51.01	16.88	70.14	9.40	52.22	9.14	35.68	8.11	24.76	5.05	16-96
N particip.	*9,113*		*2,458*		*3,607*		*2,372*		*769*		
N obs.	*81,246*		*22,293*		*33,214*		*21,005*		*4,734*		

asks respondents to rate the degree of symptoms from *less than usual* to *more than usual*. Ratings range from 0 to 36, with higher numbers indicating more severe experiences with depression. The GHQ score is a demonstrably valid and reliable instrument for detecting depression in the general population (Lundin et al., 2016).

Table 1 provides descriptive information for the analytical sample and indicates the mean value of 10.99 for the GHQ depression index. Figure 1 demonstrates the distribution patterns of GHQ score by birth cohorts. It is notable that the degree of skew differs across cohorts.

4.2 Polygenic risk score

Introduced in 2007, polygenic scores are conceptualised as a tool for quantifying the genetic contribution to phenotypes (Wray et al., 2018). For this study, a polygenic score was constructed using the recent GWAS discovery of depression from Howard et al. (2019). The construction of polygenic scores was performed using PRSice 2.0 software (Choi and O'Reilly, 2019). There were 360,140 SNPs matched after clumping between reported results in a Howard's GWAS and the UKHLS dataset. The incremental R-square is 0.4% and corresponds to the prediction from the GWAS discovery. Respondents with higher polygenic scores (measured in standard deviation units) reported more depressive symptoms during follow-up ($\beta = .046, P < .001$).

4.3 Birth cohorts

To model broad historical contexts and exposure to various shifts across different UK birth cohorts, I use the conceptualisation scheme described in Thomson and Katikireddi (2018). This scheme identifies five birth cohorts, which reflects the conventional classification of demographic cohorts for the 20th century. The first two cohorts are devoted to people exposed to the World Wars: a WWI cohort born between 1916 and 1930, and a WWII

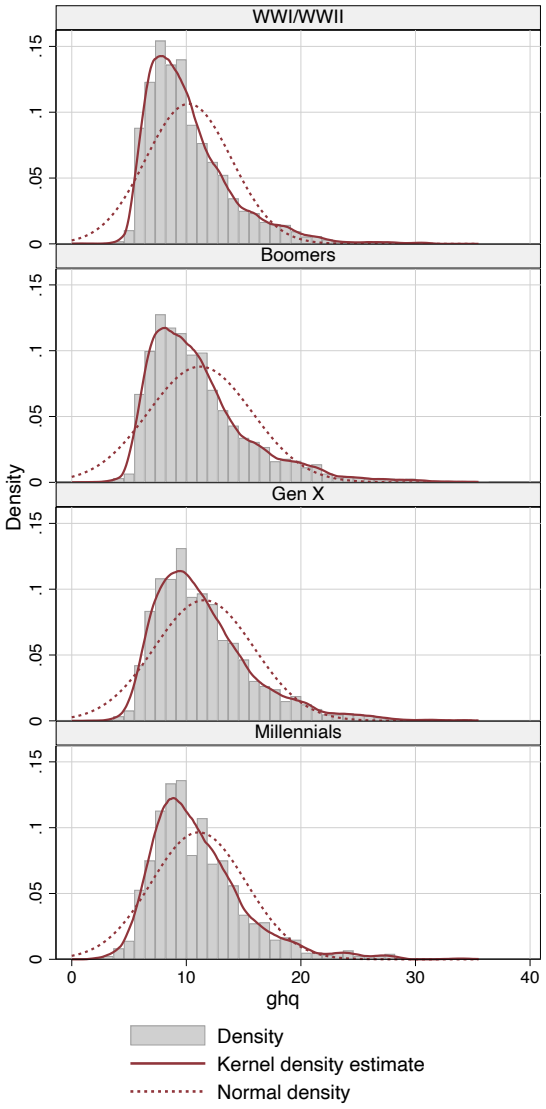

Figure 1: Distribution of GHQ depressive symptoms across birth cohorts in the UKHLS genetic sample.

cohort with birth years in 1931–1945. The demographic cohort of those born in 1946–1964 is distinguished as Boomers to reflect the postwar period of the baby boom. Thereafter, there is Generation X (people born in 1965–1980) followed by Millennials. Thomson and Katikireddi (2018) use the term 'Jilted' to describe the Millennial cohort (those born between 1981 and 1990) whereas I use the conventional term instead. As genotyping was performed in 2010, it is not feasible to include Generation Z (or Zoomers, in reference to those born in the 2000s). Due to the small number of survey participants from the WWI cohort in the UKHLS genetic sample, I merged it with the WWII cohort to create one 'World Wars' birth cohort.

4.4 Recessions

To distinguish possible trends in recessive and non-recessive historical periods, I considered the timing of survey. The periods of economic recessions are the early 1990s recession and the Great Recession). For both recessions, unemployment rates rose by minimum of 7% to peak around 10% during the hardest-hit quarters (Jenkins, 2010). For this reason, I treat the 1990 and 2008-2010 survey years as recessive.

4.5 Covariates

Distinctive sex patterns exist for depressive symptoms, so it is important to control for sex. For instance, women are more likely to be depressed than men (Kuehner, 2017). Men and women also have different ways of coping with stress (Matud, 2004).

Age is another important covariate, especially for studies of cohort trends. In Figure 2, I plot descriptive trends for the GHQ score averaged over age and cohorts. The shape is consistent with findings from Prior et al. (2020), wherein a general trend of mental health worsening with age reverses at around 50 years old before deteriorating again in older ages (after around 70). To reflect such a relationship, I include age along with its squared and cubic terms as covariates. This is also the basis for the additional scope of my sensitivity analysis. As I describe in the section to follow, the purpose of this analysis is to further disengage age and cohort trends by analysing age-comparable sub-samples. Lastly, phenotypes have an age-related genetic basis (Kulminski et al., 2016). It is thus necessary to consider age as an additional covariate in gene-by-cohorts variations.

Although I focus on respondents with European ancestry, the interaction estimates could be confounded by population stratification (Price et al., 2006). To rule out the possibility of this confounding, 20 first PCs were included as additional covariates for all models (which were provided in the release version of the data, and thus calculated by the UKHLS team).

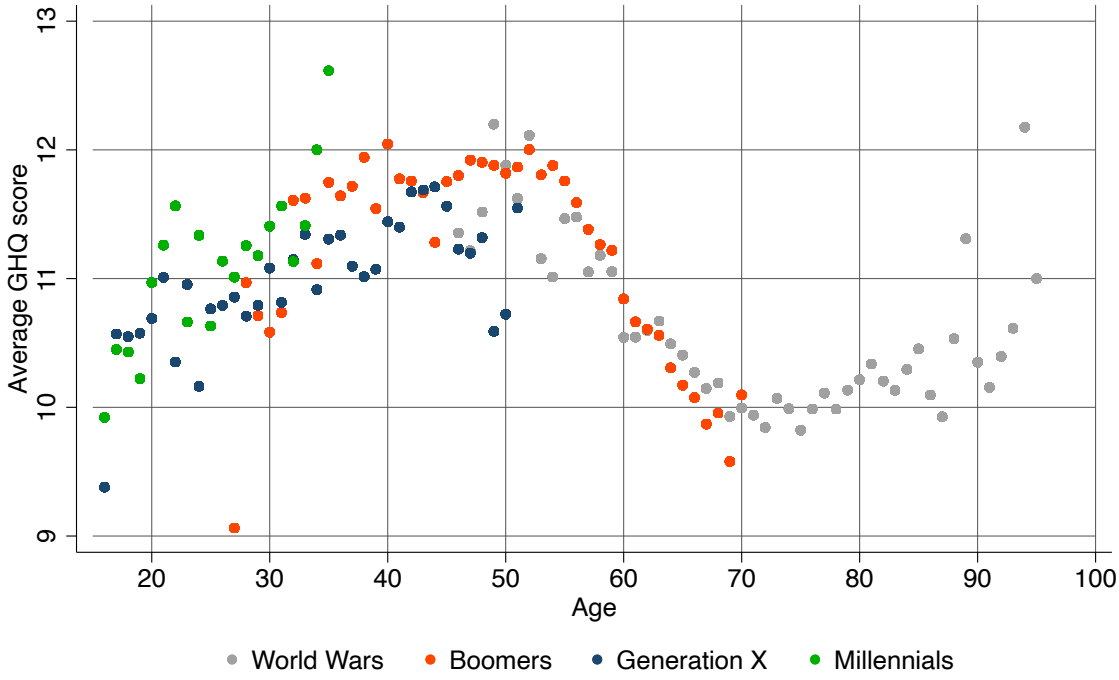

Figure 2: Average GHQ score by age, summarised by birth cohorts.

5 Empirical strategy

Gene-by-birth-cohort interactions are examined using multilevel Poisson models. The choice of model is initially determined by the nature of UKHLS data, which contains multiple observations over time. The strategy permits consideration for the correlation of repeated measurements (Hox et al., 2017; Raudenbush and Bryk, 2002). This correlation is particularly important for the depressive symptoms data.

Due to the count-based and skewed nature of the depressive symptoms scores, I employ a Poisson family of regression models. This type of model is an appropriate tool for taking the complexity of skewed data into account (Wooldridge, 2010). Moreover, it is a preferred method since the produced coefficients are more intuitive and interpretable than the OLS regression estimates with a logged dependent variable (Nichols et al., 2010).

I constructed a two-level Poisson model with the following definitions for hierarchy:

- Level 2: waves, denoted by j;
- Level 1: individuals, denoted by i.

The model is introduced as follows:

$$GHQ_{ij} \sim poisson(\mu_{ij})$$

$$log(\mu_{ij}) = \beta_0 + \beta_1 PGS_i + \beta_2 BirthCohort_i + \beta_3 PGS_i \times BirthCohort_i + \sum_p \gamma_p C_{pi} + \sum_q \gamma_q C_{qij} + u_j$$

$$var(GHQ_{ij}|\mu_{ij}) = \alpha\mu_{ij}$$

where GHQ_{ij} denotes the depression symptom score GHQ of respondent i in a wave j; μ_{ij} denotes the expected score based on a Poisson distribution; C_{pi} represents time-invariant covariates, such as sex and genetic principal components (PCs); and C_{qij} represents time-varying controls, including age and age-sq. The key parameter of interest is $_3$, which indicates the marginal association of polygenic scores for different birth cohorts. To test the modifying potential of economic downturns, I perform an analysis of three-way interactions - $PGS_i \times BirthCohort_i \times Recession_{ij}$ in Poisson models.

5.1 Gene-by-cohort analysis adjusting for age

The UKHLS is a rich source for the research questions stated earlier. As a multi-cohort longitudinal survey with an analytic period of observation spanning a quarter century, it allows me to disentangle age from cohort trends. However, one limitation is that not all ages are observed for all birth cohorts. For instance, the World Wars cohort was not observed before 45 years of age. Meanwhile, Millennials did not reach this age during data collection. Consequently, differential age distributions within each cohort have a potential to affect the accuracy of cohort estimates (Yang and Land, 2013). To address this possibility, I perform a sensitivity test where I consider age-comparable sub-samples from overlapping age groups. I am able to conduct pair-wise comparison where I first consider World Wars vs. Boomers for the ages of 46-71, Boomers vs. Generation X for 27-51 years of age, and Generation X vs. Millennials between 16-34 years old. I replicate cohort analysis following a similar statistical approach, then compare the results obtained from the entire analytic sample.

6 Results

6.1 Cohort variations in the prevalence of depressive symptoms (H1)

In terms of the research hypotheses stated earlier, Table 2 presents the results obtained from the Poisson regression models assessing cohort and gene-cohort variations in the Understanding Society genetic sample. Following the results from Model 1 in Table 2, I find evidence

of an increase in depressive symptoms occurring among people born in the second half of the 20th century. If the World Wars cohort is used as the reference category, the greatest increases occur in the cohorts of Boomers and Millennials. These results are significant at the *p=.01* level. Generation X experiences a smaller but nonetheless statistically significant increase, as well. These findings are in line with observations from Spiers et al. (2011), Spiers et al. (2012), and Rice et al. (2010). They do not provide definite support for the proposition of linear trends in the prevalence of depression across birth cohorts proposed by Bell (2014). There is no evidence of a Jilted generation hypothesis consistent with the study by Thomson and Katikireddi (2018), since the increase is observed not only for Millennials. Age and its quadratic and cubic terms display the trends described in Prior et al. (2020), which further link my findings to the existing literature.

6.2 Moderating trends of birth cohorts on the genetic association with depressive symptoms (H2)

In terms of gene-cohort moderation, Model 2 in Table 2 evidences significant positive interaction in the cohort of Baby Boomers when the earlier World Wars cohort becomes the baseline group. It is likely that the positive interactional trends are present for Generation X as well, but these results are significant at the *p=.10* level. Notably, the size of the interaction coefficient for Baby Boomers is almost the same as the coefficient for PGS. Figure 3 further illustrates this observation: the strength of the gene-phenotype correlation is greater among Boomers (i.e. participants born between 1946-1964) as the gap widens between those with a -1 and +1 standard deviation (s.d.) in genetic risk score.

The results thus show a significant and positive correlation between the polygenic score for depression and depressive symptoms in all birth cohorts. However, the strength of this correlation varies with steeper slopes occuring among Baby Boomers and Generation X. It is apparent that even though these results indicate variation in genetic penetrance among birth cohorts, they do not point to a specific conceptual model of gene $\times$ environment interactions in a definite manner. Still, the positive and significant signs of the PGS and PGS $\times$ cohort interaction estimates for Baby Boomers suggest that this birth window is likely to be a trigger component reflected in the *social trigger/compensation* G $\times$ E model.

Table 2: Coefficients and standard errors of Poisson multilevel models assessing the moderation of birth cohorts and recessions on the genetic association with depressive symptoms

	Model 1		Model 2		Model 3	
	Beta	Std. Err.	Beta	Std. Err.	Beta	Std. Err.
Cohorts (World Wars - ref.)						
Boomers	.062***	.011	.060***	.011	.059***	.012
Generation X	.039*	.016	.037*	.016	.039*	.016
Millennials	.060**	.023	.055*	.023	.059*	.023
PGS depression			.028***	.006	.032***	.007
PGS × Cohort (World Wars - ref.)						
Boomers			.025**	.009	.020*	.009
Generation X			.010	.009	.008	.010
Millennials			.019+	.012	.015	.015
Recession					.002	.006
Recession × Cohort (World Wars - ref.)						
Boomers					.011	.008
Generation X					.008	.009
Millennials					-.003	.016
Recession × PGS					-.014***	.006
Recession × PGS × Cohort (World Wars - ref.)						
Boomers					.016*	.007
Generation X					.005	.009
Millennials					.015	.017
Female	.114***	.007	.114***	.007	.114***	.007
Age	.032***	.004	.032***	.004	.032***	.004
Age^2	-.000***	.000	-.001***	.000	-.001***	.000
Age^3	.000***	.000	.000***	.000	.000***	.000
Random-Effect Var.						
$\sigma^2 u$	.093	.002	.092	.002	.092	.002
AIC	453138.9		452997.4		452991.7	
BIC	453408.8		453304.5		453373.2	
Sample Size						
No. of participants	9,113		9,113		9,113	
No. of observations	81,246		81,246		81,246	

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

Genetic score is standardised; Models include first 20 PCs as covariates

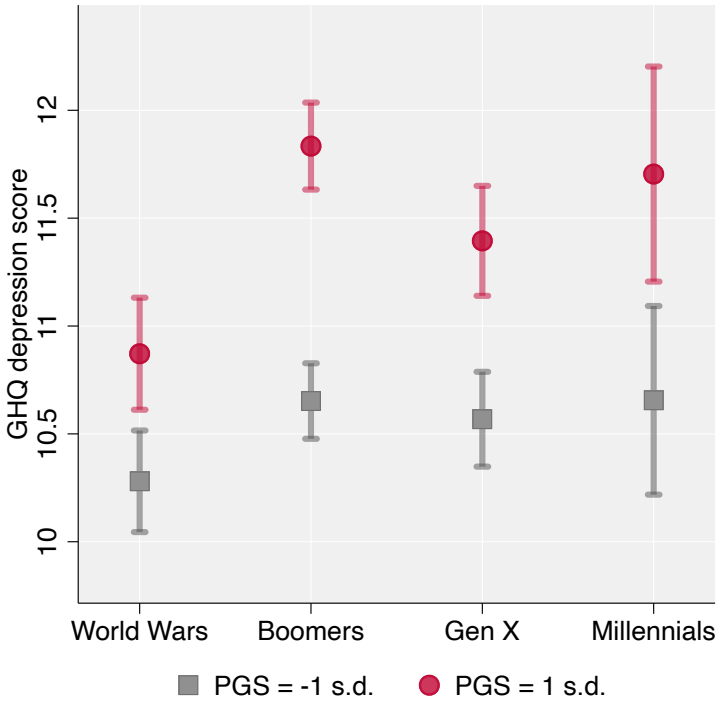

Figure 3: Birth cohorts as moderators for the association between depression polygenic risk score and depressive symptoms. Marginal probabilities from Poisson multilevel models.

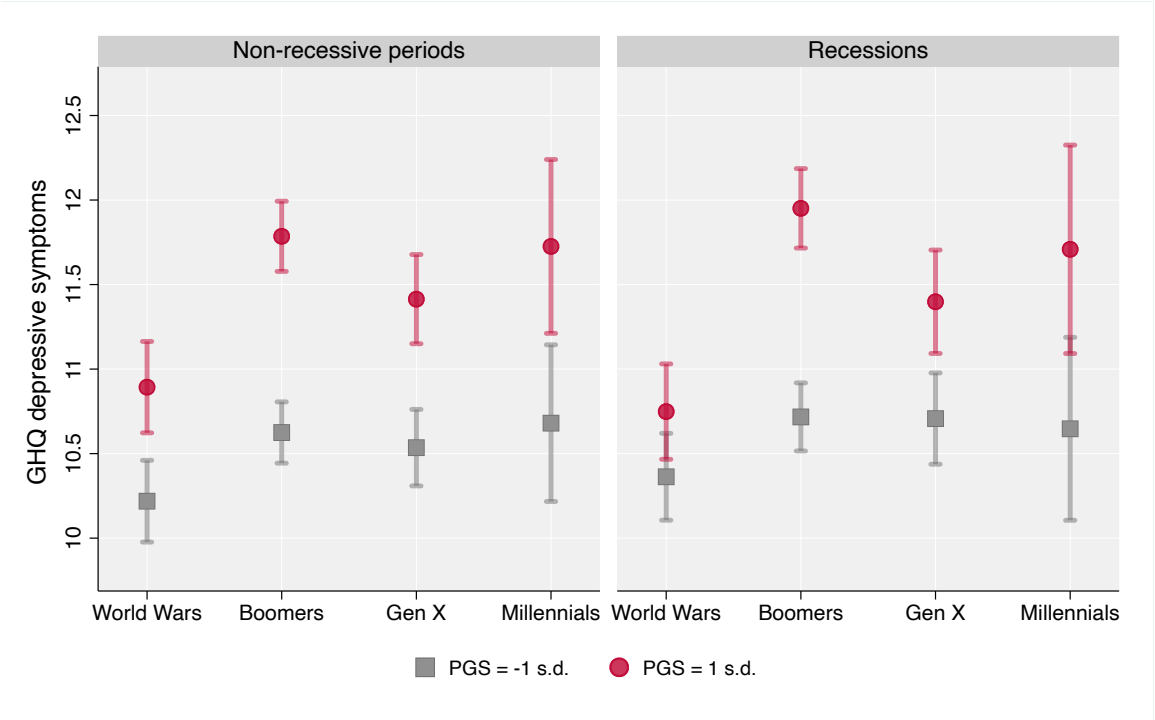

Figure 4: Birth cohorts as moderators for the association between depression polygenic risk score and depressive symptoms. Marginal probabilities from Poisson multilevel models.

6.3 Gene-by-cohort interactions during recessive and non-recessive periods (H3)

Model 3 in Table 2 and Figure 4 demonstrate the differences in the moderating patterns of birth cohorts on the genetic penetrance of depressive symptoms during recessive and non-recessive periods. Firstly, I find the polygenic prediction of depressive symptoms weakens during periods of recession; this result is statistically significant ($p < .001$ for $PGS \times recessions$ interaction term). It implies that recessions, while being exogenous economic shocks, also play the role of an environmental control. This weakens the importance of polygenic signals for a trait, which is consistent with the *social control* model from the conceptual gene $\times$ environment framework.

Moreover, I find positive three-way $PGS \times cohort \times recession$ interaction for Baby Boomers. The result is significant at the $p=.05$ level. Consistent with H3, I thus find some evidence that gene-by-cohort trends are different during times of economic downturn. In the World Wars, Generation X, and Millennials cohorts, genetic associations with depression tend to be weaker during recessions. For Baby Boomers, the gap widens between those who predisposed to depression and those who are not. This is further evidence of how historical times have the potential to shape polygenic predictions within populations

and across generations. It is also an important finding towards the notion that the same environmental condition, such as economic recession in my case, can show potential as both a social trigger and a social control for genetic penetrance (depending on the times people are born into or living in).

7 Discussions

This study examines how birth cohorts and recessions moderate genetic influence on depressive symptoms among adults in the UK. First, the paper contributes to the G×E literature in mental health research and represents an interdisciplinary research agenda. This approach to understanding mental health is necessary to provide new sets of insights. One of the challenges for the field is the absence of consistent results; effect sizes are usually small, necessitating increased power and rich data sources. This results in conceptual difficulties along with the challenge of operationalising the 'environment' in a meaningful way (see Pehkonen et al. (2017); Boardman et al. (2014) for more detailed discussion). This paper examines multiple individual observations in time to grasp trends more accurately than other G×E studies, which typically consider one environmental factor at a time. The rich set of controls and sensitivity tests aims to obtain more robust inferences. The results for the covariates are consistent with those in the existing literature.

Second, I find evidence that an increase in depressive symptoms occurred among people born in the second half of 20th century. Age-comparable analysis indicates that the increase is especially profound for Baby Boomers. Third, I do not find support for the proposition of increased genetic penetrance on depressive symptoms across all cohorts. I find evidence of increased depression prevalence in two birth cohorts, as well as significant gene-cohort moderation patterns for one of the cohorts (Baby Boomers) and suggestive moderation for the Generation X cohort. These findings are robust towards mortality selection, and marginal in the range of age-comparable robustness checks. These findings further contribute to the notion that the cohort of Baby Boomers is different from others: they achieved higher educational attainments, experienced more marital disruptions and changes in family structures that constitute their distinctive life histories (Dennis and Migliaccio, 1997) and results in greater polygenic penetrance of depression.

Lastly, I find that the polygenic prediction of depressive symptoms weakens across all birth cohorts during periods of recession – except for Baby Boomers. Thus, historical times have the potential to shape polygenic predictions within populations and across generations differently. Moreover, my findings on recessions also indicate that not only cohort-specific historical exposures can potentially shape genetic penetrance, but also historical exposures

experienced by everyone have differentiating trends.

However, I did not consider qualitative differences between birth cohorts and their experiences of different economic periods. These can be explored in further research on this topic. I also did not analyse minority samples as there is no genetic sample in the UKHLS presenting different ancestries, which is one of the most critical issues in the field of sociogenomics (see Mills and Rahal (2019) for a more detailed discussion). Future research should extend the analysis to other racial populations once data become available.

Despite these limitations, this study demonstrates that the occurrence of depressive symptoms among adults in the UK is a consequence of complex interplay among individuals' genes, incidence of birth, and the historical context of economic recession. The results illustrate the importance of applying molecular genetic data to advance our understanding of well-established links in public health and social science enquiry.

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Appendix A. Sensitivity analysis: Correction for mortality selection

Mortality selection has a potential to bias gene-by-cohort interactions (Domingue et al., 2017), so an investigation would be incomplete without correction for such potential bias. I thus expect estimates for earlier generations to be sensitive to the inclusion of weights. Below, I demonstrate the results of a Poisson regression model with the inclusion of blood weights developed by the UKHLS team to correct for differential probability to be genotyped and non-response. Moreover, blood weights provided in the UKHLS study also correct for the greatest portion of health and socio-demographic selection in the genetic sample (Akimova, 2020), these weights are expected to redress the issue sufficiently.

Table 3 displays the results obtained from the weighted Poisson regression models. Looking at columns for Models 1 and 2, it is apparent that the weighted results do not differ significantly from the main analysis. Thus, cohort variations in depressive symptoms (along with increased polygenic penetrance of depression in Boomers) are not sensitive towards the differential probability of selection for genotyping. However, weighted results on differences in the moderating patterns of birth cohorts in terms of the genetic penetrance of depression

during recessive and non-recessive periods do not display statistical significance indicating quite marginal trends (observed in the main analysis) sensitive to the implementation of weights.

Appendix B. Sensitivity analysis: Age-comparable cohort analysis

While mortality selection is one of the concerns covering a broad aspect of the UKHLS genetic sample, the findings are also likely sensitive to other plausible errors. The list of potential parameters that the findings might be sensitive to includes differential age distributions within each birth cohort, which is not taken into account (even after the inclusion of age along with its squared and cubic terms in the net of covariates). Accordingly, the following section evaluates the consistency of my findings once age-comparable cohort comparisons are applied. I show that the implication of age-comparable cohort analyses indeed changes some of my results.

Tables 4, 4, and 5 below illustrate the results of separate Poisson regressions for age-comparable sub-samples from overlapping age groups (World Wars vs. Boomers aged between 46-71, Boomers vs. Generation X aged between 27-51, and Generation X vs. Millennials aged between 16-34). What stands out in these results is the consistency of trend observed earlier, wherein Baby Boomers have higher depressive symptoms compared to the World Wars cohort. They also likely have higher scores than Generation X as well. However, it is not possible to compare Boomers with Millennials in an age-overlapping manner.

In terms of gene-cohort variations, Figure 5 graphically displays the observed trend to accompany the results tables. Following analysis of age-comparable sub-samples, the notion that genetic penetrance is greater among Baby Boomers is suggestive. But this result is significant at .10 level only; it is also unsurprising, as the estimate for the interaction term is around 30% smaller than in the main analysis and the sample size shrank as well. In line with previous results, no significant variation was observed for Generation X and Millennials.

Turning to the discussion of the role of economic downturns on genetic penetrance of depression among birth cohorts, I include Figure 6 to graphically represent my results. I find that the result of weakening polygenic prediction of depressive symptoms (during periods of recession) is also suggested in age-comparable robustness analysis. Yet the likelihood of this trend is rather marginal for Millennials, which is directly linked to the considerably smaller sample size for comparison of Generation X - Millennials. I also find the observation that genetic penetrance of depressive symptoms in Baby Boomers is stronger during recessions is robust and present in age-comparable analysis.

Table 3: Coefficients and standard errors of Poisson multilevel models assessing the moderation of birth cohorts and recessions on the genetic association with depressive symptoms correcting for differential probability to be genotyped

	Model 1		Model 2		Model 3	
	Beta	Std. Err.	Beta	Std. Err.	Beta	Std. Err.
Cohorts (World Wars - ref.)						
Boomers	.057***	.012	.056***	.012	.056***	.012
Generation X	.036*	.018	.034*	.016	.037*	.018
Millennials	.069**	.026	.064*	.023	.070*	.027
PGS depression			.028***	.007	.031***	.007
PGS × Cohort (World Wars - ref.)						
Boomers			.026**	.009	.023*	.009
Generation X			.010	.009	.010	.010
Millennials			.012	.015	.012	.016
Recession					.001	.006
Recession × Cohort (World Wars - ref.)						
Boomers					.010	.009
Generation X					.006	.011
Millennials					-.012	.020
Recession × PGS					-.009	.006
Recession × PGS × Cohort (World Wars - ref.)						
Boomers					.012	.008
Generation X					.002	.010
Millennials					.001	.022
Female	.117***	.007	.117***	.007	.117***	.007
Age	.037***	.005	.037***	.005	.036***	.005
Age^2	-.001***	.000	-.001***	.000	-.001***	.000
Age^3	.000***	.000	.000***	.000	.000***	.000
Random-Effect Variance						
$\sigma^2 u$	.091	.002	.089	.002	.089	.002
AIC	343391.8		343261.0		343263.0	
BIC	343661.5		343568.0		343644.4	
Sample Size						
No. of participants	9,113		9,113		9,113	
No. of observations	81,246		81,246		81,246	

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

Genetic score is standardised; Models include first 20 PCs as covariates

Table 4: Coefficients and standard errors of Poisson multilevel models assessing the moderation of birth cohorts and recessions on the genetic association with depressive symptoms for age-comparable cohorts [**World Wars vs. Boomers, 46-71 y.o.**]

	Model 1		Model 2	
	Beta	Std. Err.	Beta	Std. Err.
Cohorts (World Wars - ref.)				
Boomers	.035**	.012	.029*	.012
PGS depression	.034***	.008	.041***	.009
PGS × Cohort (World Wars - ref.)				
Boomers	.018+	.009	.010	.010
Recession			-.010	.008
Recession × Cohort (World Wars - ref.)				
Boomers			.025*	.010
Recession × PGS			-.020**	.008
Recession × PGS × Cohort (World Wars - ref.)				
Boomers			.025**	.009
Female	.121***	.009	.121***	.009
Age	.364***	.078	.354***	.079
Age^2	-.006***	.001	-.006***	.001
Age^3	.000***	.000	.000***	.000
Random-Effect Variance				
^2u	.098	.002	.098	.002
AIC	216914.6		216900.7	
BIC	217163.6		217184.1	
Sample Size				
No. of participants	5,205		5,205	
No. of observations	39,562		39,562	

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

Genetic score is standardised; Models include first 20 PCs as covariates

Table 5: Coefficients and standard errors of Poisson multilevel models assessing the moderation of birth cohorts and recessions on the genetic association with depressive symptoms for age-comparable cohorts [**Boomers vs. Generation X, 27-51 y.o.**]

	Model 1		Model 2	
	Beta	Std. Err.	Beta	Std. Err.
Cohorts (Boomers - ref.)				
Generation X	-.025*	.012	-.028*	.012
PGS depression	.041***	.008	.046***	.008
PGS × Cohort (Boomers - ref.)				
Generation X	-.004	.010	-.008	.011
Recession			-.000	.009
Recession × Cohort (Boomers - ref.)				
Generation X			.013	.011
Recession × PGS			-.017+	.008
Recession × PGS × Cohort (Boomers - ref.)				
Generation X			.009	.011
Female	.111***	.010	.111***	.010
Age	.010	.050	.005	.050
Age^2	-.000	.001	.000	.001
Age^3	-.000	.000	-.000	.000
Random-Effect Variance				
^2u	.088	.002	.088	.002
AIC	190336.1		190331.9	
BIC	190579.7		190609.1	
Sample Size				
No. of participants	4,178		4,178	
No. of observations	32,890		32,890	

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

Genetic score is standardised; Models include first 20 PCs as covariates

Table 6: Coefficients and standard errors of Poisson multilevel models assessing the moderation of birth cohorts and recessions on the genetic association with depressive symptoms for age-comparable cohorts [**Generation X vs. Millennials, 16-34 y.o.**]

	Model 1		Model 2	
	Beta	Std. Err.	Beta	Std. Err.
Cohorts (Generation X - ref.)				
Millennials	.011	.017	.012	.018
PGS depression	.033**	.010	.038**	.011
PGS × Cohort (Generation X - ref.)				
Millennials	.014	.016	.010	.017
Recession			-.003	.014
Recession × Cohort (Generation X - ref.)				
Millennials		-.006	.020	
Recession × PGS			-.015	.014
Recession × PGS × Cohort (Generation X - ref.)				
Millennials			.015	.021
Female	.111***	.016	.111***	.016
Age	.191**	.073	.189*	.074
Age^2	-.007*	.003	-.007*	.003
Age^3	.000*	.000	.000*	.000
Random-Effect Variance				
^2u	.086	.004	.086	.004
AIC	70242.2		70247.5	
BIC	70456.6		70491.5	
Sample Size				
No. of participants	1,847		1,847	
No. of observations	11,997		11,997	

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

Genetic score is standardised; Models include first 20 PCs as covariates

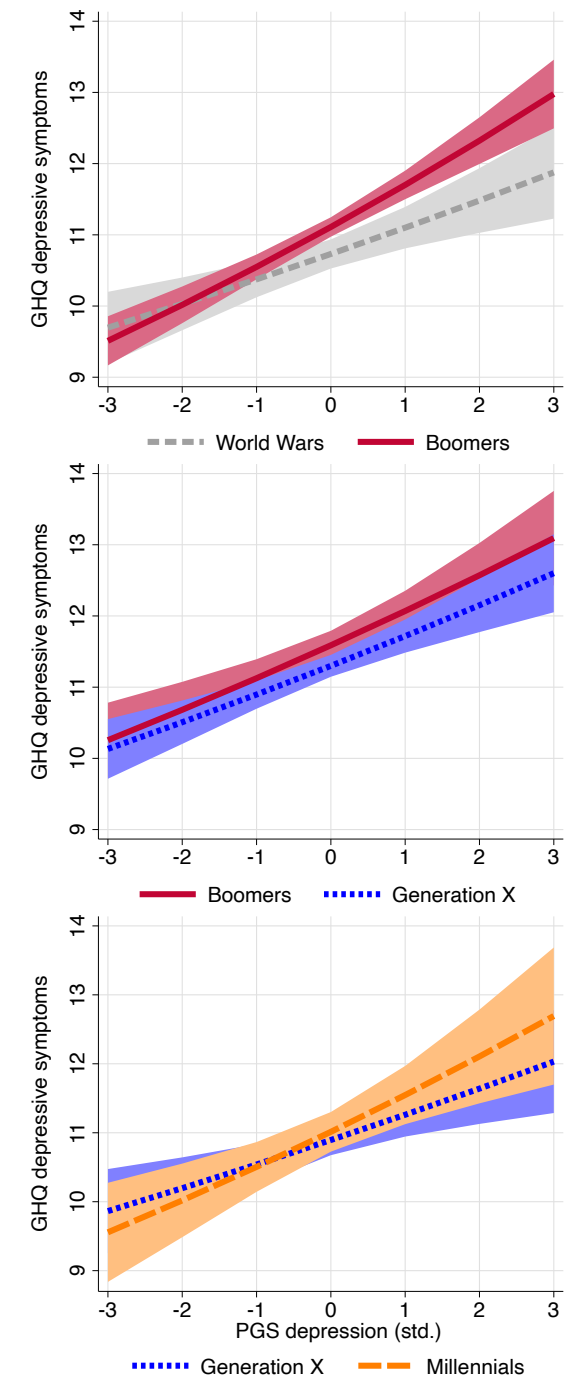

Figure 5: Birth cohorts as moderators for the association between depression polygenic risk score and depressive symptoms. Marginal probabilities from Poisson multilevel models.

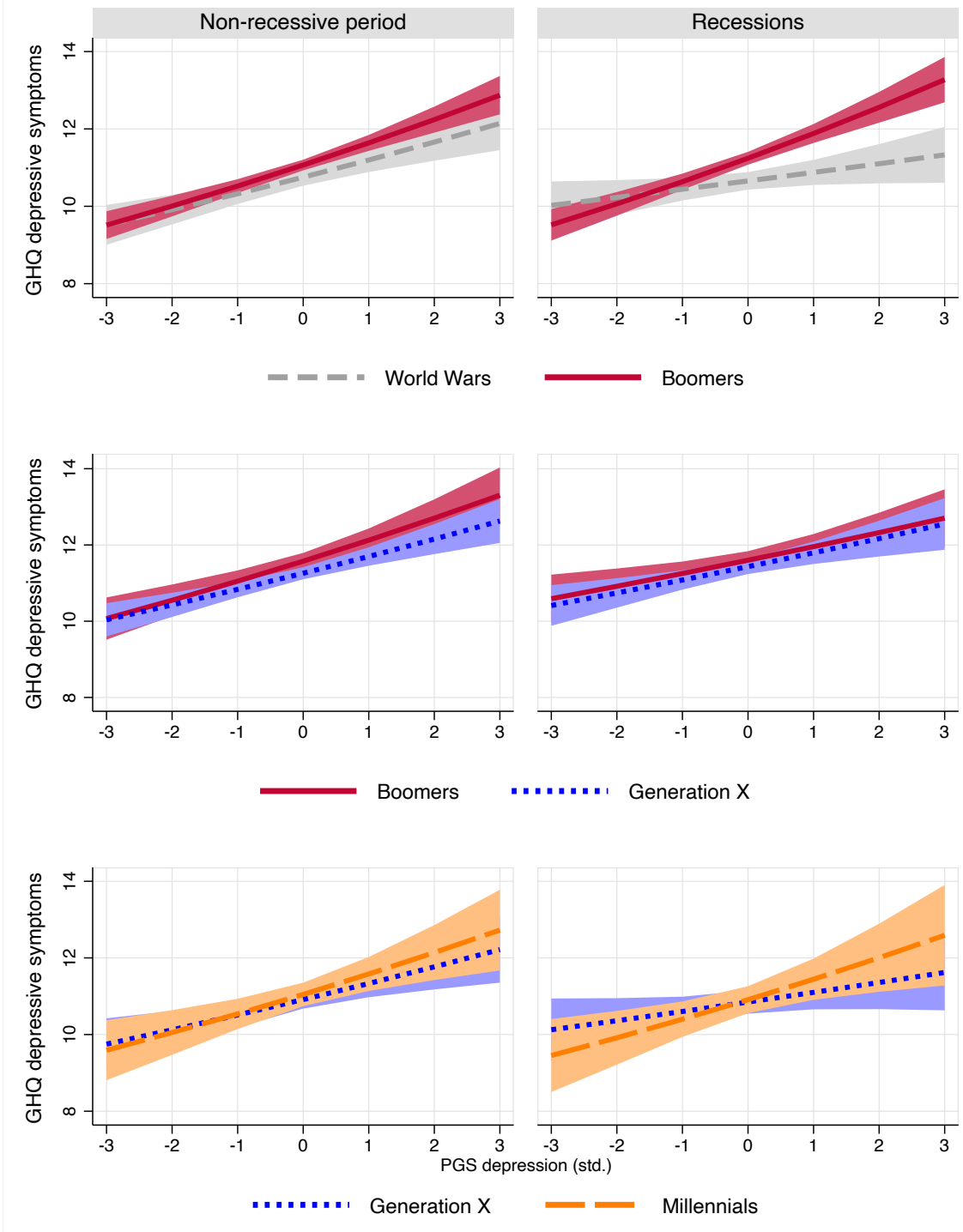

Figure 6: Birth cohorts as moderators for the association between depression polygenic risk score and depressive symptoms. Marginal probabilities from Poisson multilevel models.