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Abstract

This study explored the interplay between genetic predisposition, partnership status and depression by examining the association of a polygenic risk score (PGS) for depression with time to antidepressant purchasing and the moderating role of partnership status. We analysed data from 30,192 Finnish individuals with an accelerated failure time model. While the cumulative hazard of antidepressant purchasing varied across PGS and partnership status – with the highest cumulative hazard in the widowed group, followed by divorced, single, married and cohabiting – we found no evidence for an interaction between PGS and partnership status. Results were robust to different model specifications, gender stratification, choice of PGS, and endogenous selection. Although antidepressant purchasing correlated with both PGS and partnership status, we found no evidence that partnership status could partially offset or amplify the association between the PGS for depression and depression incidence.

Introduction

In Europe, about 7% of the population above the age of 25 suffer from chronic depression.[1] The prevalence of depression increased in recent decades with more recent cohorts exhibiting depression at an earlier age at onset.[2] This might be partially attributed to the increasing individualization in modern societies that leads to increased competition, inequality, social isolation and loneliness.[2]

Consequently, changes in social relationships might be of particular importance in explaining the rise in depression prevalence.[3] Social relationships, indicated by higher levels of perceived social support, diverse social networks and higher social connectedness, are associated with a lower risk for depression.[4] Being married or in a partnership are important forms of social relationships[3], and are associated with lower levels of depression through increased resources to cope with stressors.[5,6] Furthermore, individuals who live with others benefit from their respective social networks compared to living alone. This might provide additional resources for building social networks and social support.[4]

Depression is a result of both environmental and genetic influences.[7] It is partly genetically heritable with heritability estimates ranging from 8% in SNP-based heritability[8] to 40% heritability in twin and family studies.[7] Research from genome-wide association studies (GWAS) indicate that depression is a polygenic trait that is influenced by a large number of genetic variants each contributing a small effect.[8-13] These polygenic associations can be combined into a polygenic risk score (PGS) to assess their joint contribution on depression.[14] Lu et al[14] report an increased odds for major depressive disorder (MDD) diagnosis of about 1.3 with one standard deviation increase in the PGS for depression.

The way in which social relationships affect depression risk is not fully understood, and the combined analysis of social and genetic factors may provide valuable insights into underlying mechanisms of this relationship.[12,13,15] According to the differential susceptibility theory (DST)[16], individuals with an unfavourable polygenic risk for depression might be more susceptible to both positive and negative environmental influences, such as entering marriage or experiencing divorce. This, in turn, affects their susceptibility to develop depression.[13,17,18] However, the previous results on the link between the genetic risk for depression and the role of social relationships are mixed. Twin studies consistently report that genetic influences on depression are amplified by social isolation, and reduced by social support and being married,[19-22] but observational research finds mixed evidence for an interaction between the polygenic risk for

depression and stressful life events, social support, partnership status and other social relationship indicators.[23-26]

Most previous research is conducted on samples smaller than 10,000, which might not provide adequate statistical power to detect gene-environment interactions (GxE).[18] Furthermore, partnership status might not only affect the overall depression risk but also the time until incident depression. In line with DST, we hypothesize that individuals who have an unfavourable genetic risk profile for developing depression may particularly benefit from cohabiting or being married. This might partly offset their genetic susceptibility to depression and delay incident depression, compared to individuals with an unfavourable genetic risk profile who are single, divorced or widowed. We add to existing literature by investigating to what extent the link between the polygenic risk for depression and time to antidepressant purchasing is moderated by partnership status in a nationally representative sample of the Finnish population.

Results

Sample Characteristics

Sample characteristics at baseline can be found in Table 1. We followed 30,192 people (15,771 females and 14,421 males) over a mean follow-up period of 12.9 (SD: 6.1) years. At baseline, participants were on average 50 (SD:13.34) years old. Of the people who were followed up, 23.4% purchased antidepressants after a mean follow-up of 7.1 (SD: 5.3) years. Stratified by PGS percentiles, 29.3% of participants in the 80th PGS percentile purchased antidepressants during follow up, followed by 23.1% in the 21st to 79th percentile and 18.7% in the 20th percentile. Among partnership status groups, divorced participants most often purchased antidepressants, followed by single, widowed, cohabiting and married.

Table 1 Sample characteristics at baseline overall and for participants purchased antidepressants (AD) during the follow-up period. SD: standard deviation.

	Overall: 30,192	Purchased AD: 23.4%
	mean (SD)	
Time to event or censoring	12.9 (6.1)	7.1 (5.3)
Age	50.2 (13.3)	48.9 (12.8)
	N	%
Percentiles of the PGS based on Howard et al.		
<=20th	6187	18.7
21st to 79th	18154	23.1
>=80th	5851	29.3
Percentiles of the PGS based on Wray et al.		
<=20th	6169	19.9
21st to 79th	18091	23.2
>=80th	5932	27.9
Sex		
Female	15771	27.7
Male	14421	18.8
Education		
basic level education	8713	24.2
secondary	11180	23.3
lower tertiary	4766	25.1
tertiary	2539	21.2

higher tertiary	2994	21.0
Partnership status		
married, registered partnership or separated	18421	22.6
divorced	3724	28.3
widowed	1437	21.7
cohabiting	2647	21.5
single (not cohabiting or married)	3963	24.9
Sample Collection		
FINRISK 1992	4063	28.4
FINRISK 1997	5946	27.3
FINRISK 2002	5954	25.0
FINRISK 2007	4305	21.1
FINRISK 2012	4300	12.7
HEALTH 2000	5012	25.3
HEALTH 2011	612	14.5

Error! Reference source not found. Participants in the 80th PGS percentile or above had a higher cumulative probability of antidepressant purchasing with a steeper slope across follow-up in all partnership status groups, compared to the 20th and 21st to 79th PGS percentiles (Figure 1). The cumulative probability of antidepressant purchasing was lowest in the 20th PGS percentile for all partnership status groups, though curves for the 20th and 21st to 79th percentile overlap in the cohabiting group. The wider spread among the polygenic risk percentiles in the divorced group may indicate moderation.
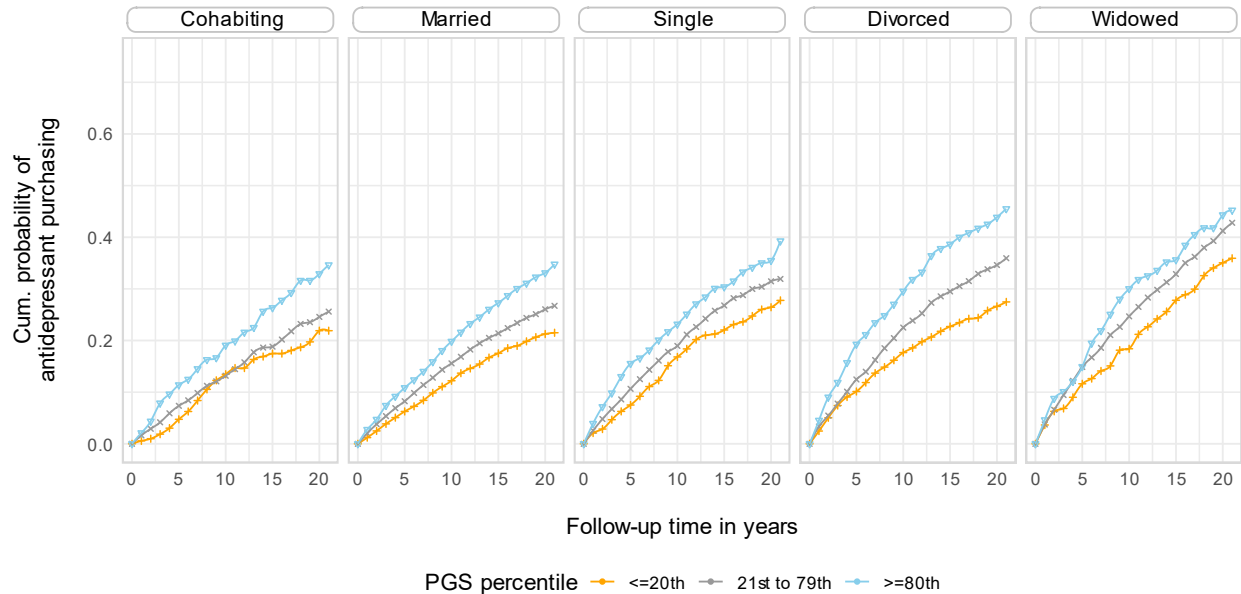
Figure 1 Crude cumulative probability $(1 - S(t))$ of antidepressant purchasing by percentiles of polygenic risk score and partnership status across follow-up time.

Cumulative hazard of antidepressant purchasing by polygenic risk and partnership status

Adding an interaction term did not significantly improve model fit for Model 2 compared to Model 1 (p=0.59) and Model 3.2 and Model 3.1 (p=0.58), i.e. we did not find sufficient evidence for an interaction term (supplementary Table S.1). The coefficients for model specifications 1, 2, 3.2 and 4 can be found in supplementary Table S.2.

Figure 2 shows the predicted cumulative hazard of antidepressant purchasing at follow-up year 10 for the PGS percentiles by partnership status for four sets of confounder adjustment (Model 1, 2, 3.2 and 4) (see also supplementary Table S.3). In model 1, we found larger predicted cumulative hazards, i.e. accumulated risk of antidepressant purchasing, for the 80th PGS percentile than for the 20th and 21st to 79th PGS percentile across all partnership status groups. Being widowed was associated with the largest cumulative hazard at year 10 of 0.2 (95% CI: 0.17-0.23) in the 20th and 0.34 (95% CI: 0.28-0.39) in the 80th PGS percentile, followed by divorced (*20th PGS perc:* 0.18 (95% CI: 0.15-0.20); *80th PGS perc:* 0.30 (95% CI: 0.26-0.34)), single (*20th PGS perc:* 0.16 (95% CI: 0.14-0.18); *80th PGS perc:* 0.27 (95% CI: 0.23-0.31)), married (*20th PGS perc:* 0.13 (95% CI: 0.11-0.14); *80th PGS perc:* 0.22 (95% CI: 0.19-0.24)) and cohabiting (*20th PGS perc:* 0.11 (95% CI: 0.1-0.13); *80th PGS perc:* 0.19 (95% CI: 0.16-0.23)). After introducing an interaction term between partnership status and the PGS (Model 2) and additionally adjusting for education (Model 3.2), we found only marginal differences in the predicted cumulative hazard

across PGS percentiles and partnership status categories compared to Model 1. Adjustment according to Keller (Model 4) resulted in marginal changes in the predicted cumulative hazard and more uncertainty compared to the other model specifications.
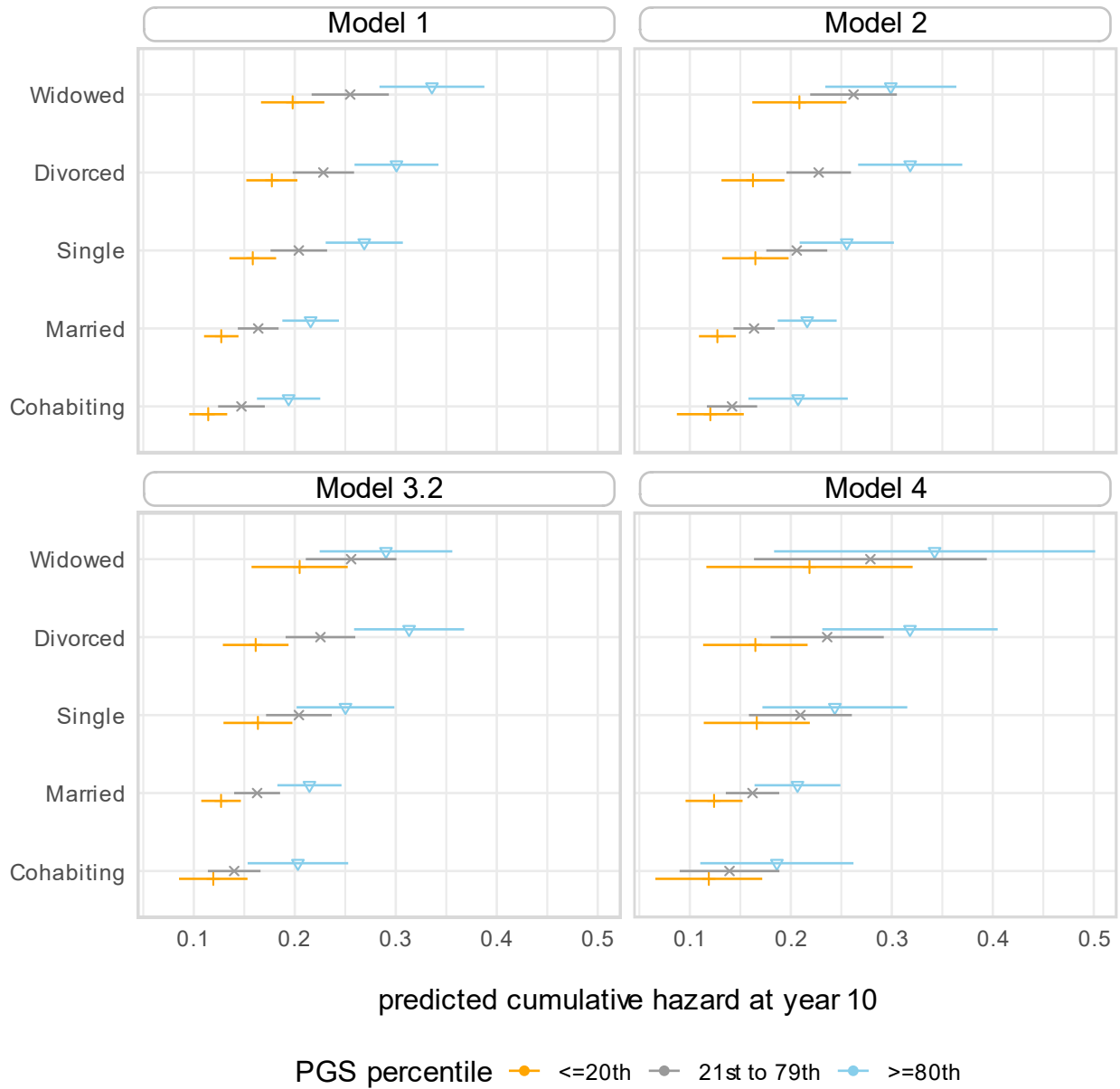
Figure 2 Predicted cumulative hazard of antidepressant purchasing at follow-up year 10 for polygenic risk score percentiles and partnership status. Model 1 includes PGS, partnership status, age, sex, batch/sample and population structure PCs. Model 2 includes an interaction term between PGS and partnership status. Model 3: Model 2 with education, Model 4: Model 3 with Keller adjustment.

Figure 3 shows the predicted cumulative hazard of antidepressant purchasing across follow-up for the 20th, 21th to 79th, and 80th PGS percentile by partnership status based on Model 3.2. We found larger predicted cumulative hazards for the 80th than for the 20th PGS percentile in all partnership status groups. The divorced groups showed the largest increase in the predicted cumulative hazard of antidepressant purchasing across follow-up time.
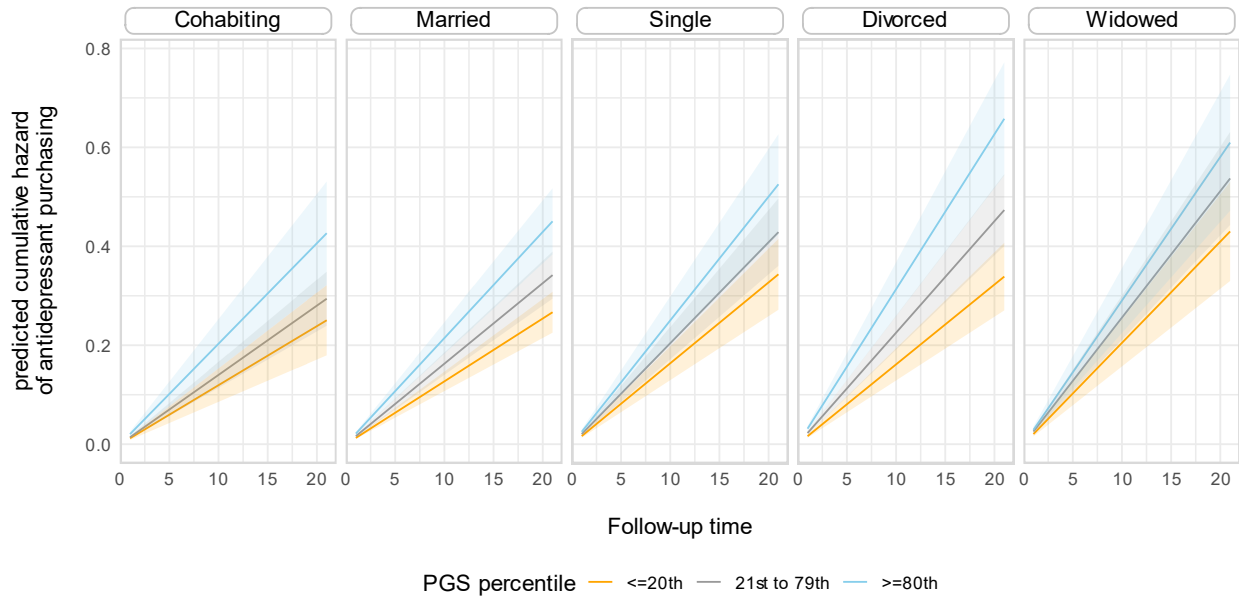
Figure 3 Predicted cumulative hazard of antidepressant purchasing across follow-up time by PGS percentiles and partnership status. Predictions based on Model 3.2.

Sensitivity analysis

Stratified by gender, we find a larger predicted cumulative hazard of antidepressant purchasing at follow-up year 10 in women compared to men for all PGS and partnership status groups except for widowed men in the 20th PGS percentile, though confidence intervals overlap (supplementary Figure S.1 and Table S.4). Adjustment according to Keller[27] (Model 4) resulted in more uncertainty compared to the other model specification (Model 3.2).

We repeated the analysis with a PGS based on a GWAS from Wray et al.[10] with model specifications 3 and 4. This resulted in marginal differences in the predicted cumulative hazard of antidepressant purchasing compared to the main analysis, and the same conclusions as the main analysis (supplementary Figure S.2 and Table S.5).

Discussion

Our study found that the predicted cumulative hazard of antidepressant purchasing was larger among participants in the 80th PGS percentile compared to the 20th PGS percentile among all partnership status groups in Finnish adults aged between 25 to 80 years. Among partnership status groups, widowed had the highest cumulative hazard of antidepressant purchasing, followed by divorced, single, married and cohabiting. We found no evidence that partnership status moderates the link between the polygenic risk for depression and time to antidepressant purchasing. Model adjustment resulted in only marginal changes in effect estimates. We found modest differences in the interaction between PGS and partnership status across gender. Sensitivity analysis suggested that the results are robust to the choice of the polygenic risk score for depression.

An advantage of our study was the use of the FINRISK and HEALTH surveys which can be linked with the Finnish registry and medication database. This allowed for a yearly follow-up with detailed information on antidepressant medication use, no missingness on partnership status and covariates, no self-report bias and no loss to follow-up. Furthermore, with the available sample size of above 30,000 individuals, we had more statistical power than previous studies, which allow us to be more confident in our conclusions regarding the presence of GxE between partnership status and antidepressant purchasing.

The PGS in our main analysis was based on a GWAS which includes self-reported depressive symptoms and depression diagnosis as the outcome.[8] Including self-reported questions on depression may reduce the predictive power of the PGS to predict MDD but it allowed for studying a larger sample size since self-reported depression is more commonly available in cohort studies than depression diagnosis.[28] Furthermore, a PGS built on a broader definition of depression may give insight into how depressive symptoms can develop as secondary affects, for example through susceptibility to environmental exposures, which is of interest in our study.[29] While the predictive power of a polygenic risk score might differ depending on which genetic variants are included[30], sensitivity analysis revealed that our results are robust to the choice of variants to be included in the polygenic risk score and the definition of depression (supplementary Figure S.2).

Antidepressant purchasing requires a medical practitioner's prescription but is not a diagnosis of depression as such. In Finland, primary care is responsible for the treatment of mild to moderate depression with the recommendation to prescribe antidepressants for acute depression,[31] resulting in about 50% of antidepressants being prescribed by doctors with no specialty.[32]

Possibly as a result of that, about one quarter of Finnish individuals who take antidepressants have no diagnosed mental disorder.[33] On the other hand, antidepressant use is not affected by self-reported biases compared to survey-based measures of depression. Nonetheless, using antidepressant purchasing as a proxy for depression may overestimate actual depression diagnosis, which might lead to an underestimation of the relationship between the PGS and depression and the interaction of partnership status with the PGS.

Another consideration is that according to Keller[27], confounding of the interaction term needs to be controlled for by including all covariate-by-environment and covariate-by-gene interaction terms. While this might yield a more precise coefficient of the interaction term of interest, this approach comes at the cost of more uncertainty (because of the large number of interaction terms that require more statistical power) and lower interpretability (because of the large number of coefficients that cannot be interpreted independently). It is important to note that interpreting solely the coefficient of interest without taking the main term and other interaction terms into account might lead to incorrect conclusions in regards to the effect size and uncertainty. We addressed this by showing predicted cumulative hazards instead of coefficients.

Furthermore, our sensitivity analysis found that there is evidence for endogenous selection into divorce based on the PGS (supplementary Table S.6). This might introduce collider bias and could lead to an inflated interaction coefficient and over-interpretation of the magnitude of interaction.[34] Although this needs to be considered when interpreting the main and interaction terms found for the divorced group, our conclusions of no evidence for an interaction between PGS and partnership remain the same. Nonetheless, it is important to consider endogenous selection when conducting GxE studies for depression because the polygenic risk for depression might not only affect the biological risk of developing depression but also affect an individuals' behaviour and choices regarding their environments. Future research with interest in GxE might benefit from using 4-way decompositions[35] to disentangle the effects of mediation (introduced through endogenous selection) and interaction.

This study found that partnership status and the PGS are independently associated with antidepressant purchasing. These results were in line with Stringa et al.[26] who find no evidence for GxE interaction between partnership status, network size and received emotional support with depression or depressive symptoms. Several twin studies, on the other hand, found evidence for moderation. Nes et al.[22] reported that the part of subjective well-being that is explained by genetics is smaller among married and cohabiting compared to single respondents. Beam et al[20] found similar results for married compared to divorced and never married respondents. Findings may

differ depending on whether a twin sample or a general population sample was used for a few reasons. First of all, twin research takes a different methodological approach to investigating GxE interactions compared to research on the general population. Whereas studies in the general population often investigate the interaction between a polygenic risk score and a phenotype in regression models, twin research makes use of variance components models to determine the presence of GxE interactions.[36] Second, twin models are based on different assumptions such as no assortative mating and the equal environment assumption which makes them less generalizable to the general population.[18] Lastly, heritability estimates from twin samples are higher than for SNP-based or PGS heritability.[7,8,18] Larger heritability results in a larger power to detect interaction effects. These differences might explain why findings on the general population do not align with findings from twin studies.

The beneficial link of partnership status with depression may depend on other individual and contextual factors[37] which might affect the moderating effect of partnership status on the genetic susceptibility to depression. First, the association between partnership status and mental health might depend on the perceived quality of the relationship or marriage. Indeed, South et al.[38] find evidence for a moderating effect of marital satisfaction on the association between polygenic risk and anxiety symptoms in a general population sample. Second, experiencing a divorce or widowhood is a stressful life event, and marriage or cohabitation may be defined as life change events.[39] Stressful life events were repeatedly examined as a potential moderator for the link between genetic effects and psychiatric disorders with mixed results depending on the sample and genetic variant(s) examined.[13,23,24] The association between experiencing a stressful life event and mental health is strongest around the time that the event occurred.[40-42] Consequently, the moderating effect of partnership status on genetic susceptibility to depression might depend on the relationship quality, relationship duration and time since partnership status change. Future research might benefit from combining structural and subjective indicators for social relationships and investigating possible anticipation and adaptation effects of partnership status transitions to assess the moderating effect of social relationships on the genetic susceptibility to depression.

To conclude, we found no evidence for partnership status moderating the effects of genetic susceptibility to depression on depression incidence. In other words, we found no evidence that being married or cohabiting could partially offset the genetic susceptibility to depression. Instead, both partnership status and genetic susceptibility are independent predictors of depression onset.

Methods

Data Source

We performed our analysis with genetic data from the Finnish Institute for Health and Welfare (THL) Biobank. Genetic information was obtained from blood samples as part of the clinical examinations for the FINRISK and HEALTH surveys. The FINRISK surveys conducted health examinations in participants aged 25 to 74 years, residing in seven selected geographical areas in Finland. For our analysis, we included the FINRISK surveys conducted in 1992, 1997, 2002, 2007 and 2012. In 1992, the participation rate was 72% in men and 81% in women and declined to 57% in men and 67% in women in 2012.[43] The HEALTH survey included a sample of the Finnish population above the age of 30 collected in 2000 and 2011. Participation rate was 89% in 2000 and 67.3% 2011.[44,45] We linked FINRISK and HEALTH survey data to the Finnish national registers, which contain individual-level demographic and socioeconomic information on individuals permanently residing in Finland. The participants were followed up each calendar year. We subsequently linked the data with the Finnish Social Insurance Institution's Prescription Register, which contained individual-level information on outpatient prescription medication from 1997 onwards.

Study Population (Inclusion/Exclusion criteria)

We studied a cohort of individuals residing in Finland between ages 25 and 80 years. The flowchart for sample selection can be found in supplementary Figure S.3. We restricted our sample to 37,355 individuals who have register and genetic information. We excluded participants who purchased antidepressant medication in the period of two years before the start of follow-up. We defined the start of follow-up as 1999 for participants of FINRISK in 1992 and in 1997 (because data on medication use is available from 1997 onwards) and as the year when the survey was conducted for the other FINRISK and HEALTH surveys. We included participants who have register data past baseline (N=33,241) and excluded 2,922 individuals who are classified as 1st or 2nd degree relatives of other participants based on a genetic relatedness indicator π̂ of above 0.1875.[46] We furthermore excluded 127 individuals with interval censoring. We followed up individuals until 2019 or until censoring occurred. The final analytic sample was 30,192 individuals.

Outcome

We defined antidepressant purchasing as at least one purchase of an antidepressant (ATC N06A) and/or an antidepressant in combination with psycholeptics (ATC N06CA) in a given calendar year from the Finnish Social Insurance Institution's Prescription Register.

Genetic Risk

For the main analysis, we constructed a PGS that is based on a GWAS by Howard et al.[47] This GWAS used a broad definition of depression (diagnosed MDD and self-reported depression) as the outcome and analysed 246,363 cases and 561,190 controls. The sample included the UK biobank, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium (PGC) cohorts and the 23and Me sample. For constructing the polygenic risk score, we excluded the 23and Me samples due to privacy policies.

The polygenic risk score was adjusted for linkage disequilibrium using SBayesR method, the summary statistics of Howard et al.[47] and the linkage disequilibrium matrix provided by the authors of the method. These re-weighted scores were summed to individual PGSs using autosomal HapMap3 variants with MAF >0.01. We categorized the PGS into <=20th percentile, 21st to 79th percentile and >=80th percentile.

Partnership status

We measured partnership status at baseline and each follow-up year as obtained from the population register. Partnership status was classified into single (not married or cohabiting); cohabiting; married, in a registered partnership or separated; divorced; and widowed. We classified individuals as cohabiting if they lived in the same dwelling with a partner of opposite sex, who was not a married spouse or a sibling and with whom the age difference did not exceed 15 years.

Confounders

We assessed gender and education at baseline, and age each follow-up year. Education was categorized into basic level education (not completing further degrees beyond basic level); secondary (upper secondary level or post-secondary non-tertiary education); lower tertiary (short-cycle tertiary education); tertiary (bachelor's or equivalent level) and higher tertiary education (master's or doctoral education or equivalent level). Population structure was adjusted for with 10 first principal components (PCs) of the genome. We also adjusted for the genotyping batch and data collection round.

Statistical Analysis

We employed an accelerated failure time (AFT) model to assess the relationship between the PGS for depression with cumulative incidence of antidepressant purchasing across follow-up time, and the moderating effect of partnership status. We modelled partnership status and age as time-varying. We chose an AFT model instead of a proportional hazard-based model because AFT models avoid the non-collapsibility and resulting selection bias of proportional hazard-based models.[48,49] We assessed whether the Weibull, exponential, lognormal or log-logistic distribution was an appropriate choice for the error distribution by plotting the predicted survival probability from each distribution against the crude survival probability. Based on supplementary Figure S.4, we deem the exponential distribution to be the best fit as it most accurately approximates the observed data at the beginning and end of follow-up.

We first fit a model that includes the PGS and partnership status without an interaction term, controlling for age, sex, batch/sample and PCs of population structure (Model 1) (Table 2). In a second model (Model 2), we introduced an interaction term between PGS and partnership status to assess the presence of moderation. In a third model, we additionally adjusted for education (Model 3). Keller[27] notes that adjusting for confounders by simply adding them as covariates in the model will not control for possible confounding of the interaction term if covariates interact with the polygenic risk score and/or partnership status. Instead, confounders need to be included as covariate-by-environment and covariate-by-gene interaction terms. We therefore fit an additional model (Model 4) in which we control for gender, age and education by including PGS-covariate and partnership status-covariate interaction terms. We performed a loglikelihood ratio test and compare Model 1 with Model 2, and Model 3 with and without an interaction term (Model 3.2 versus Model 3.1) to test whether the interaction term significantly improves model fit. We did not perform a likelihood ratio test for Model 4 with and without an interaction term, since the confounder adjustment according to Keller is only applied to adjust for confounding of the interaction term. We presented the predicted cumulative hazard at follow-up year 10 ($H(10)$) for each partnership status category for each PGS percentile group. The cumulative hazard can be defined as the accumulated risk of purchasing antidepressants up until time t.[50] It can be obtained from the survival probability $S(t)$ as $H(t) = -\log(S(t))$. For predictions, PCs of population structure were held constant at the mean. Predictions obtained from Model 1 and 2 were averaged over age, sex and data/batch. For Model 3.2 and 4, they were additionally averaged over education. We performed subgroup analysis by gender.

Table 2 Model specifications.

Model	Model specification
1	PGS + partnership status + age + sex + batch/sample + population structure (PCs)
2	PGS * partnership status + age + sex + batch/sample + population structure (PCs)
3.1	***Model 1*** + education
3.2	***Model 2*** + education
4	PGS*(partnership status + age + sex + education) + partnership status*(age + sex + education) + batch/sample + population structure (PCs)

Sensitivity Analysis

For sensitivity analysis, we repeated the analysis with a PGS based on a GWAS conducted by Wray et al.[10]. This PGS was based on a stricter definition of depression (MDD diagnosis only) but a smaller sample size with 135,458 cases and 344,901 controls.[10] The GWAS did not include data on Finnish individuals. We aimed to investigate whether the predictive power of predicting antidepressant purchasing is larger for the PGS by Wray et al.[10] and whether the strength of GxE interactions differs compared with the PGS based on Howard et al.[47]

While partnership status might moderate the relationship between genetic susceptibility to depression and antidepressant purchasing, there is a possibility for self-selection into or out of a certain partnership status based on the PGS. In the presence of this type of selection bias and unobserved confounding of the partnership – antidepressant purchasing relationship, partnership status becomes a collider, which introduces a new path from the PGS to partnership status to antidepressant purchasing. This could lead to biased coefficients of the interaction term between PGS and partnership status.[34] We assessed whether endogenous selection bias might be present by fitting a nominal multinomial Generalized Estimating Equation (GEE) model with partnership status as the outcome and the PGS based on Howard et al. as the predictor. We fit a GEE model to take the longitudinal structure of the data, i.e. multiple observations per individual, into account (Supplement Table S.6).

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Supplementary material to "Genetic susceptibility to depression and the role of partnership status"

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Main Analysis

Table S. 1 Likelihood Ratio Test for Model 1 compared to Model 2 and Model 3.1 to Model 3.2.

model	DF	Loglikelihood	Df	Test statistic	p-value
M1 compared to M2	33	-35199.95	8	6.57	0.59
	41	-35196.67			
M3.1 compared to M3.2	36	-35186.71	8	6.72	0.58
	44	-35183.35			

Table S. 2 AFT Model coefficients and 95%Confidence Interval for different model specifications. Coefficients and 95%CI are exponentiated and can be interpreted as acceleration factors (in reference to the reference categories of other covariates).

	Model 1		Model 2		Model 3.2		Model 4	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
PGS								
<21st	Ref.							
21st to 79th	1.29	1.21-1.37	1.28	1.18-1.40	1.28	1.17-1.40	1.62	1.08-2.42
>=80th	1.70	1.57-1.83	1.70	1.54-1.88	1.69	1.53-1.87	2.87	1.82-4.54
Partnership status								
Married	Ref.							
Divorced	1.39	1.31-1.49	1.28	1.08-1.51	1.27	1.08-1.50	3.19	2.09-4.87
Widowed	1.56	1.42-1.70	1.64	1.34-2.00	1.61	1.32-1.97	2.03	0.93-4.43
Cohabiting	0.90	0.81-1.00	0.94	0.73-1.22	0.94	0.73-1.21	1.99	1.05-3.77
Single	1.25	1.16-1.34	1.29	1.09-1.54	1.29	1.08-1.53	2.30	1.52-3.50
PGS*partnership								
21st to 79th * divorced	-	-	1.09	0.91-1.31	1.09	0.91-1.31	1.08	0.89-1.30
>=80th * divorced	-	-	1.15	0.94-1.42	1.15	0.93-1.42	1.11	0.90-1.37
21st to 79th * widowed	-	-	0.98	0.78-1.23	0.97	0.78-1.22	0.98	0.77-1.25
>=80th * widowed	-	-	0.84	0.64-1.11	0.84	0.64-1.10	0.93	0.70-1.24
21st to 79th * cohabiting	-	-	0.92	0.69-1.22	0.92	0.69-1.22	0.89	0.66-1.19
>=80th * cohabiting	-	-	1.01	0.73-1.41	1.01	0.72-1.40	0.91	0.65-1.29
21st to 79th * single	-	-	0.97	0.80-1.18	0.97	0.80-1.19	0.95	0.78-1.16
>=80th * single	-	-	0.91	0.72-1.15	0.91	0.72-1.14	0.86	0.68-1.09
age	1.00	0.99-1.00	1.00	0.99-1.00	0.99	0.99-1.00	1.00	1.00-1.01
SEX: female	1.46	1.39-1.53	1.46	1.39-1.53	1.46	1.39-1.54	1.55	1.37-1.76
Education								
Secondary	-	-	-	-	0.87	0.82-0.93	0.97	0.83-1.14
Lower tertiary	-	-	-	-	0.90	0.84-0.97	1.01	0.83-1.23

Tertiary	-	-	-	-	0.87	0.78-0.96	0.88	0.68-1.15
Higher tertiary	-	-	-	-	0.82	0.75-0.90	0.96	0.76-1.21
PGS-Covariate Interaction terms								
21st to 79th * SEX:female	-	-	-	-	-	-	1.01	0.88-1.15
>=80th * SEX:female	-	-	-	-	-	-	0.89	0.77-1.05
21st to 79th *age	-	-	-	-	-	-	1.00	0.99-1.00
>=80th *age	-	-	-	-	-	-	0.99	0.99-1.00
21st to 79th * Education: secondary	-	-	-	-	-	-	0.89	0.75-1.05
>=80th * Education: secondary	-	-	-	-	-	-	0.94	0.78-1.15
21st to 79th * Education: lower tertiary	-	-	-	-	-	-	0.87	0.71-1.08
>=80th * Education: lower tertiary	-	-	-	-	-	-	0.94	0.75-1.19
21st to 79th * Education: tertiary	-	-	-	-	-	-	1.05	0.80-1.39
>=80th * Education: tertiary	-	-	-	-	-	-	0.85	0.61-1.18
21st to 79th * Education: higher tertiary	-	-	-	-	-	-	0.86	0.67-1.10
>=80th * Education: higher tertiary	-	-	-	-	-	-	0.74	0.55-1.00
Partnership status-Covariate interaction terms								
Divorced * SEX:female	-	-	-	-	-	-	0.94	0.82-1.07
Widowed * SEX:female	-	-	-	-	-	-	0.70	0.57-0.86
Cohabiting * SEX:female	-	-	-	-	-	-	1.03	0.83-1.27
Single * SEX:female	-	-	-	-	-	-	0.98	0.84-1.14
Divorced * age	-	-	-	-	-	-	0.99	0.98-0.99
Widowed * age	-	-	-	-	-	-	1.00	0.99-1.01
Cohabiting * age	-	-	-	-	-	-	0.99	0.98-1.00
Single * age	-	-	-	-	-	-	0.99	0.98-0.99
Divorced * Education: secondary	-	-	-	-	-	-	0.87	0.74-1.02
Widowed * Education: secondary	-	-	-	-	-	-	1.16	0.94-1.43
Cohabiting * Education: secondary	-	-	-	-	-	-	0.78	0.58-1.04
Single * Education: secondary	-	-	-	-	-	-	1.06	0.87-1.29
Divorced * Education: lower tertiary	-	-	-	-	-	-	0.81	0.67-0.99
Widowed * Education: lower tertiary	-	-	-	-	-	-	1.31	0.99-1.75

Cohabiting * Education: lower tertiary	-	-	-	-	-	-	0.87	0.62-1.22
Single * Education: lower tertiary	-	-	-	-	-	-	1.02	0.80-1.30
Divorced* Education: tertiary	-	-	-	-	-	-	0.83	0.63-1.10
Widowed* Education: tertiary	-	-	-	-	-	-	1.07	0.68-1.68
Cohabiting* Education: tertiary	-	-	-	-	-	-	0.77	0.51-1.17
Single * Education: tertiary	-	-	-	-	-	-	1.17	0.87-1.56
Divorced* Education: higher tertiary	-	-	-	-	-	-	0.86	0.66-1.14
Widowed* Education: higher tertiary	-	-	-	-	-	-	1.25	0.81-1.93
Cohabiting* Education: higher tertiary	-	-	-	-	-	-	0.91	0.60-1.39
Single* Education: higher tertiary	-	-	-	-	-	-	1.14	0.86-1.51
Population Structure								
pc1	0.44	0.02-10.71	0.44	0.02-10.64	0.32	0.01-7.82	0.38	0.02-9.36
pc2	0.03	0.00-0.77	0.03	0.00-0.78	0.03	0.00-0.80	0.03	0.00-0.75
pc3	51.77	1.98-1354.78	50.85	1.94-1330.49	57.48	2.2-1501.24	53.00	2.02-1390.27
pc4	1.22	0.05-28.96	1.23	0.05-29.15	1.17	0.05-27.71	1.19	0.05-28.32
pc5	0.68	0.03-16.2	0.70	0.03-16.69	0.83	0.03-19.67	0.88	0.04-21.10
pc6	6.21	0.25-154.42	6.24	0.25-155.27	7.32	0.3-181.51	6.99	0.28-173.5
pc7	0.44	0.02-10.88	0.43	0.02-10.64	0.43	0.02-10.48	0.45	0.02-11.04
pc8	1.63	0.07-38.13	1.64	0.07-38.60	2.04	0.09-47.73	2.39	0.10-55.97
pc9	3.09	0.12-77.22	3.27	0.13-81.65	3.45	0.14-85.98	3.41	0.14-85.19
pc10	0.16	0.01-3.96	0.16	0.01-4.02	0.17	0.01-4.29	0.17	0.01-4.21
Data/Batch								
Broad_HEALTH	0.94	0.76-1.17	0.94	0.76-1.17	0.93	0.75-1.16	0.94	0.75-1.16
Corogene_FINRISK	1.00	0.79-1.26	1.00	0.79-1.26	0.99	0.78-1.25	1.00	0.79-1.26
Engage_FINRISK	0.91	0.73-1.13	0.91	0.73-1.12	0.90	0.72-1.11	0.9	0.73-1.12
FIMM_HEALTH	0.94	0.72-1.22	0.93	0.72-1.22	0.93	0.72-1.21	0.95	0.73-1.23
Finpcga_FINRISK	1.00	0.81-1.24	1.00	0.81-1.23	0.99	0.80-1.22	1.00	0.81-1.23
FR02_BROAD_FINRISK	0.96	0.76-1.21	0.96	0.76-1.21	0.95	0.75-1.20	0.95	0.76-1.21
FR12_FINRISK	0.95	0.76-1.2	0.95	0.75-1.20	0.96	0.76-1.21	0.96	0.76-1.21
FR12AFFY_FINRISK	0.95	0.74-1.22	0.95	0.74-1.22	0.96	0.75-1.23	0.97	0.75-1.24

Genmets_HEALTH	0.95	0.76-1.19	0.95	0.76-1.19	0.94	0.75-1.18	0.95	0.76-1.19
MRPRED_FINRISK	1.06	0.85-1.32	1.05	0.84-1.32	1.03	0.83-1.29	1.04	0.83-1.30
PalotieCoreExome_FINRISK	0.92	0.74-1.14	0.91	0.73-1.14	0.91	0.73-1.13	0.91	0.73-1.13
predictCVD_FINRISK	1.21	0.96-1.52	1.21	0.96-1.51	1.18	0.94-1.49	1.19	0.95-1.49
SUMMIT_FINRISK	1.24	0.95-1.62	1.24	0.95-1.62	1.22	0.94-1.59	1.23	0.94-1.60

Table S. 3 Predicted cumulative hazard at follow-up year 10 ($H(10)$) and 95% confidence interval for different model specifications, stratified by PGS and partnership status.

PGS	Partnership status	Model 1		Model 2		Model 3.2		Model 4	
		H(t)	95%CI	H(t)	95%CI	H(t)	95%CI	H(t)	95%CI
<=20th	cohabiting	0.11	(0.10-0.13)	0.12	(0.09-0.15)	0.12	(0.09-0.15)	0.12	(0.07-0.17)
	divorced	0.18	(0.15-0.20)	0.16	(0.13-0.19)	0.16	(0.13-0.19)	0.16	(0.11-0.22)
	married	0.13	(0.11-0.14)	0.13	(0.11-0.15)	0.13	(0.11-0.15)	0.12	(0.10-0.15)
	single	0.16	(0.14-0.18)	0.16	(0.13-0.20)	0.16	(0.13-0.20)	0.17	(0.11-0.22)
	widowed	0.20	(0.17-0.23)	0.21	(0.16-0.26)	0.20	(0.16-0.25)	0.22	(0.12-0.32)
21st to 79th	cohabiting	0.15	(0.12-0.17)	0.14	(0.12-0.17)	0.14	(0.11-0.17)	0.14	(0.09-0.19)
	divorced	0.23	(0.20-0.26)	0.23	(0.2-0.26)	0.23	(0.19-0.26)	0.24	(0.18-0.29)
	married	0.16	(0.14-0.18)	0.16	(0.14-0.18)	0.16	(0.14-0.19)	0.16	(0.14-0.19)
	single	0.20	(0.18-0.23)	0.21	(0.18-0.24)	0.20	(0.17-0.24)	0.21	(0.16-0.26)
	widowed	0.25	(0.22-0.29)	0.26	(0.22-0.31)	0.26	(0.21-0.30)	0.28	(0.16-0.39)
>=80th	cohabiting	0.19	(0.16-0.23)	0.21	(0.16-0.26)	0.20	(0.15-0.25)	0.19	(0.11-0.26)
	divorced	0.30	(0.26-0.34)	0.32	(0.27-0.37)	0.31	(0.26-0.37)	0.32	(0.23-0.4)
	married	0.22	(0.19-0.24)	0.22	(0.19-0.25)	0.21	(0.18-0.25)	0.21	(0.16-0.25)
	single	0.27	(0.23-0.31)	0.26	(0.21-0.30)	0.25	(0.2-0.30)	0.24	(0.17-0.32)
	widowed	0.34	(0.28-0.39)	0.30	(0.23-0.36)	0.29	(0.22-0.36)	0.34	(0.18-0.50)

Subgroup & Sensitivity Analysis

Figure S. 1 Predicted cumulative hazard of antidepressant purchasing at follow-up year 10 for polygenic risk score percentiles and partnership status by sex. Model 3 includes interaction term between PGS and partnership status, age, batch/sample, education and population structure PCs. Model 4: Model 3 with Keller adjustment.

Table S. 4 Predicted cumulative hazard at follow-up year 10 (H(10)) and 95% confidence interval for different model specifications, stratified by PGS and partnership status and sex. Model 3 includes interaction term between PGS and partnership status, age, batch/sample, education and population structure PCs. Model 4: Model 3 with Keller adjustment.

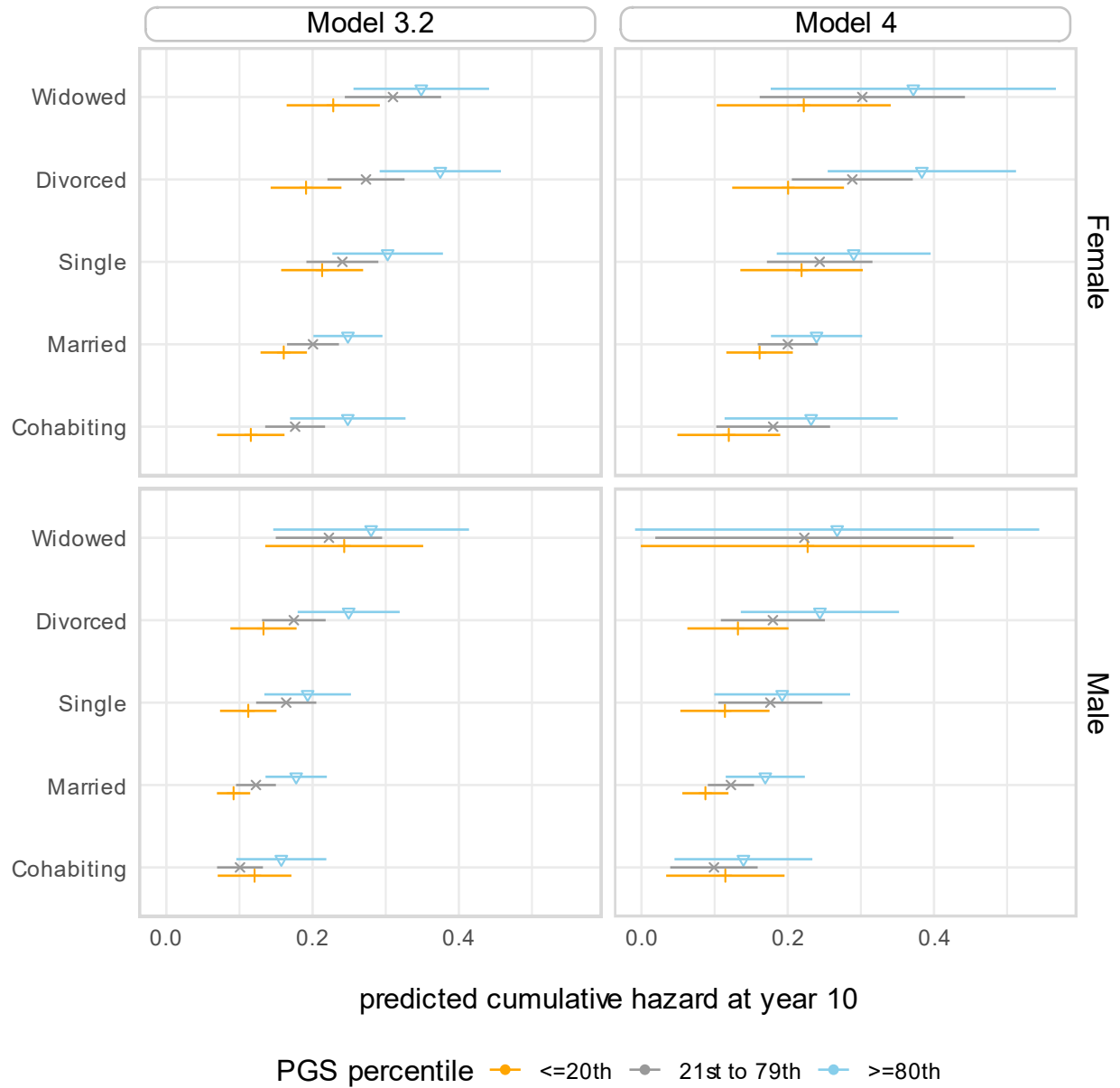| PGS	partnership status	Model 3.2		Model 4	
		H(10)	95%CI	H(10)	95%CI
Female					
<=20th	cohabiting	0.12	(0.07-0.16)	0.12	(0.05-0.19)
	divorced	0.19	(0.14-0.24)	0.20	(0.12-0.28)
	married	0.16	(0.13-0.19)	0.16	(0.12-0.21)
	single	0.21	(0.16-0.27)	0.22	(0.14-0.30)
	widowed	0.23	(0.16-0.29)	0.22	(0.10-0.34)
21st to 79th	cohabiting	0.18	(0.14-0.22)	0.18	(0.10-0.26)
	divorced	0.27	(0.22-0.33)	0.29	(0.21-0.37)
	married	0.20	(0.17-0.24)	0.20	(0.16-0.24)
	single	0.24	(0.19-0.29)	0.24	(0.17-0.32)
	widowed	0.31	(0.24-0.38)	0.30	(0.16-0.44)
>=80th	cohabiting	0.25	(0.17-0.33)	0.23	(0.11-0.35)
	divorced	0.37	(0.29-0.46)	0.38	(0.25-0.51)
	married	0.25	(0.20-0.30)	0.24	(0.18-0.30)
	single	0.30	(0.23-0.38)	0.29	(0.18-0.40)
	widowed	0.35	(0.26-0.44)	0.37	(0.18-0.57)
Male					
<=20th	cohabiting	0.12	(0.07-0.17)	0.11	(0.03-0.20)
	divorced	0.13	(0.09-0.18)	0.13	(0.06-0.20)
	married	0.09	(0.07-0.11)	0.09	(0.06-0.12)
	single	0.11	(0.07-0.15)	0.11	(0.05-0.18)
	widowed	0.24	(0.14-0.35)	0.23	(0.00-0.46)
21st to 79th	cohabiting	0.10	(0.07-0.13)	0.10	(0.04-0.16)
	divorced	0.17	(0.13-0.22)	0.18	(0.11-0.25)
	married	0.12	(0.10-0.15)	0.12	(0.09-0.15)
	single	0.16	(0.12-0.21)	0.18	(0.11-0.25)
	widowed	0.22	(0.15-0.30)	0.22	(0.02-0.43)
>=80th	cohabiting	0.16	(0.10-0.22)	0.14	(0.05-0.23)
	divorced	0.25	(0.18-0.32)	0.24	(0.14-0.35)
	married	0.18	(0.14-0.22)	0.17	(0.12-0.22)
	single	0.19	(0.13-0.25)	0.19	(0.10-0.29)
	widowed	0.28	(0.15-0.41)	0.27	(-0.01-0.54)

PGS based on GWAS by Wray et al.
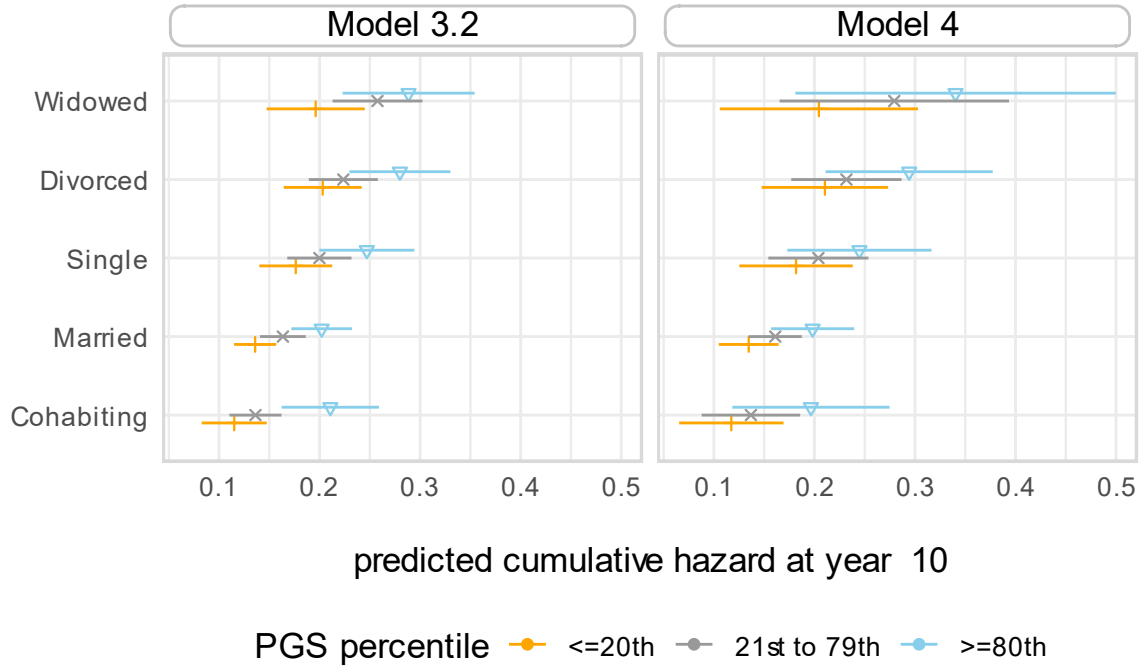
Figure S. 2 Predicted cumulative hazard of antidepressant purchasing at follow-up year 10 for polygenic risk score percentiles based on Wray et al. and partnership status. Model 3 includes interaction term between PGS and partnership status, age, sex, batch/sample, education and population structure PCs. Model 4: Model 3 with Keller adjustment.

Table S. 5 Predicted cumulative hazard at follow-up year 10 (H(10)) and 95% confidence interval for different model specifications, stratified by PGS based on Wray et al. and partnership status. Model 3 includes interaction term between PGS and partnership status, age, sex, batch/sample, education and population structure PCs. Model 4: Model 3 with Keller adjustment.

PGS	Partnership status	Model 3.2		Model 4	
		H(10)	95%CI	H(10)	95%CI
<=20th	cohabiting	0.12	(0.08-0.15)	0.12	(0.07-0.17)
	divorced	0.20	(0.16-0.24)	0.21	(0.15-0.27)
	married	0.14	(0.11-0.16)	0.13	(0.10-0.16)
	single	0.18	(0.14-0.21)	0.18	(0.13-0.24)
	widowed	0.20	(0.15-0.24)	0.20	(0.11-0.30)
21st to 79th	cohabiting	0.14	(0.11-0.16)	0.14	(0.09-0.19)
	divorced	0.22	(0.19-0.26)	0.23	(0.18-0.29)
	married	0.16	(0.14-0.19)	0.16	(0.13-0.19)
	single	0.20	(0.17-0.23)	0.20	(0.15-0.25)
	widowed	0.26	(0.21-0.30)	0.28	(0.17-0.39)
>=80th	cohabiting	0.21	(0.16-0.26)	0.20	(0.12-0.27)
	divorced	0.28	(0.23-0.33)	0.29	(0.21-0.38)
	married	0.20	(0.17-0.23)	0.20	(0.16-0.24)
	single	0.25	(0.20-0.29)	0.24	(0.17-0.32)
	widowed	0.29	(0.22-0.35)	0.34	(0.18-0.50)

Table S. 6 Sensitivity check for selection into marriage. Coefficients (exponentiated) and standard errors (not exponentiated) from nominal multinomial GEE model. Coefficients are in reference to the single category.

Sensitivity check for selection into partnership status					
	Partnership status				
	Married	Divorced	Widowed	Cohabiting	Single
Intercept	5.17***	1.19***	0.52***	0.61***	Ref.
	(0.018)	(0.022)	(0.027)	(0.025)	
PGS based on Howard et al.	1.00	1.07**	0.98	1.01	Ref.
	(0.02)	(0.02)	(0.03)	(0.02)	
Observations	396,403				
Number of individuals	30,192				
Note:	*p<0.05**p<0.01***p<0.001				

```
┌─────────────────────────┐
│ N individuals in FINRISK │
│   and HEALTH surveys:    │          ┌──────────────────────────────┐
│                          │─────────▶│ no genetic information: 5,250 │
│         42,605           │          └──────────────────────────────┘
└─────────────────────────┘
            │
            ▼
┌─────────────────────────┐
│ genetic information:     │          ┌──────────────────────────────┐
│       37,355             │─────────▶│ no register data available: 3 │
└─────────────────────────┘          └──────────────────────────────┘
            │
            ▼
┌─────────────────────────┐
│ linked to register data: │          ┌──────────────────────────────┐
│       37,352             │─────────▶│ exclude non-eligible ages:   │
└─────────────────────────┘          │            15                │
            │                         └──────────────────────────────┘
            ▼
┌─────────────────────────┐
│ observations >=age 25    │          ┌──────────────────────────────┐
│   and <= age 80:         │─────────▶│ purchased AD during 2-year   │
│                          │          │ inclusion period:            │
│       37,337             │          │          3,344               │
└─────────────────────────┘          └──────────────────────────────┘
            │
            ▼
┌─────────────────────────┐
│ No AD purchasing during  │          ┌──────────────────────────────┐
│ 2-year inclusion period: │─────────▶│ No register data available   │
│                          │          │ from baseline onwards:       │
│       33,993             │          │           752                │
└─────────────────────────┘          └──────────────────────────────┘
            │
            ▼
┌─────────────────────────┐
│ register data available  │          ┌──────────────────────────────┐
│ from baseline onwards:   │─────────▶│ genetically 1st or 2nd degree│
│                          │          │ relatives:                   │
│       33,241             │          │          2,922               │
└─────────────────────────┘          └──────────────────────────────┘
            │
            ▼
┌─────────────────────────┐
│ not genetically related: │          ┌──────────────────────────────┐
│                          │─────────▶│ Interval censoring: 127      │
│       30,319             │          └──────────────────────────────┘
└─────────────────────────┘
            │
            ▼
┌─────────────────────────┐
│ no interval censoring:   │
│                          │
│       30,192             │
└─────────────────────────┘
```

Figure S. 3 Flowchart for sample selection.

Weibull distribution

Exponential distribution

Loglogistic distribution
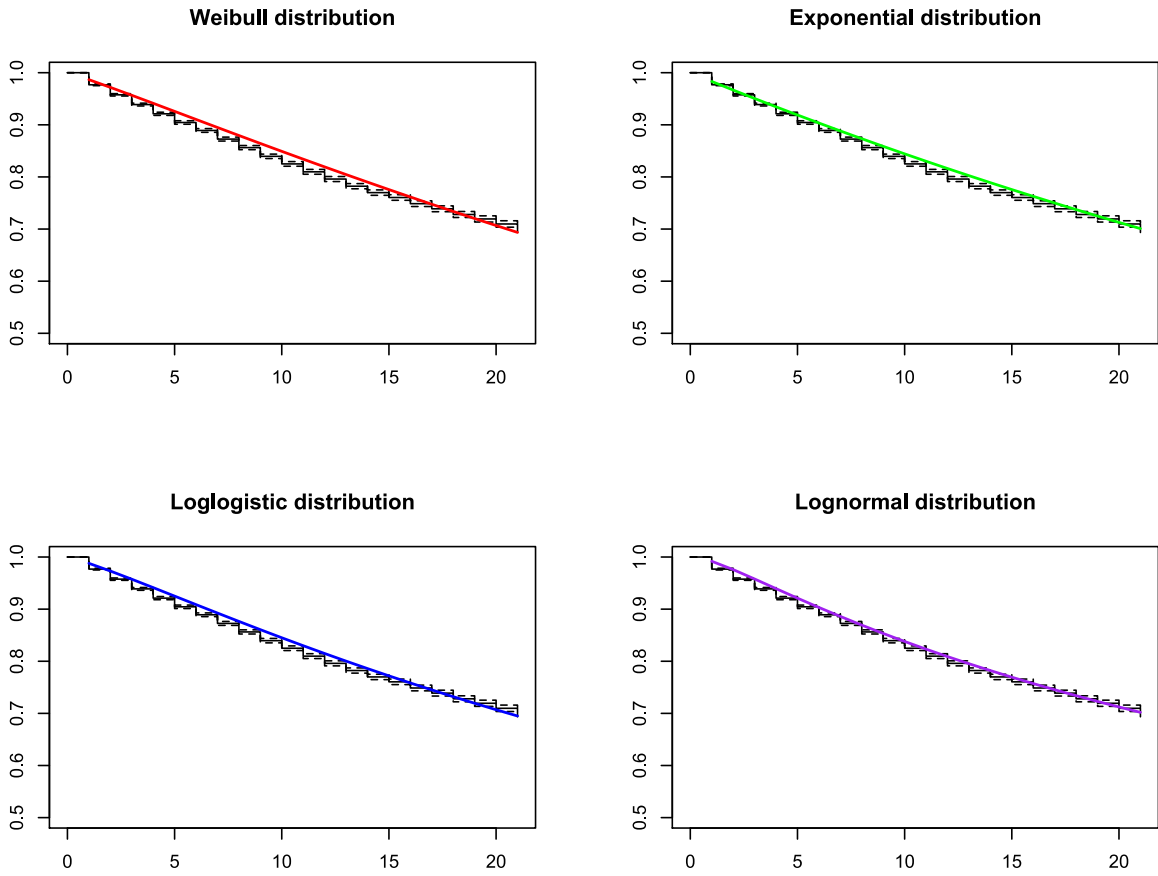
Lognormal distribution

Figure S. 4 Different error distributions for Model 3 plotted against the observed data across follow-up time. We deem exponential to be the best fit as it is most accurate at the beginning and end of follow-up time.