# Genetic susceptibility to depression and the role of partnership status

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**Abstract**

**Background:** Social relationships and genetic predisposition are known to affect depression risk, but their joint effects are poorly understood. We investigate to what extent the link between the polygenic risk for depression and time to antidepressant purchasing is moderated by partnership status.

**Methods:** We study 30,192 Finnish individuals that participated in the FINRISK and HEALTH surveys and have register and medication data available. We assess genetic risk with a polygenic risk score (PGS) for depression. Depression was assessed through whether an individual purchased antidepressants at least once in the past year. We perform an accelerated failure time model with partnership status as time-varying and different sets of confounder adjustment.

**Results:** 23.4% of individuals purchased antidepressants during follow-up. Including only the main terms for PGS and partnership status, being widowed is associated with the largest cumulative incidence of 19.97 (95%CI: 16.65-22.93) in the 20$^{th}$ and 33.58 (95%CI: 28.39-38.77) in the 80th PGS percentile at year 10, followed by divorced, single, married and cohabiting. Including an interaction term between PGS and partnership status results in only marginal changes in the predicted cumulative hazard. Results are robust to different model specifications, gender stratification, the choice of PGS, and selection into partnership status based on the PGS (endogenous selection bias).

**Conclusion:** While we found antidepressant purchasing to be associated with PGS and partnership status, we did not find evidence for an interaction between these factors.

## 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 onset.[2] This might be attributed to the increasing individualization in modern societies that leads to increased competition, inequality, social isolation and loneliness.[2]

Consequently, 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] Therefore, partnership status may often indicate the presence of social support, social networks and social connectedness.

Depression is a result of both environmental and genetic influences.[7] Depression is partly genetically heritable with heritability estimates of depression ranging from 8% 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 genetic variants each contributing a small effect.[8-13] These polygenic associations can be combined into a polygenic 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 SD increase in PGS for depression.

The way in which social relationships affect depression risk is not fully understood, and the combined analysis of social and genetics factors may provide valuable insights into underlying mechanisms of how these factors interact.[12,13,15] According to the differential susceptibility theory (DST), individuals with an unfavourable polygenic risk for depression might be more susceptible to be affected by both positive and negative environmental influences, such as entering marriage or experiencing divorce. This, in turn, affects their susceptibility to develop depression.[13,16,17] However, the previous results on the link between the polygenic 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 marital status,[18-21] 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.[22-25]

Most previous research is conducted on samples smaller than 10,000, which might not provide adequate statistical power to detect gene-environment interactions (GxE).[17] Furthermore, partnership status might not only affect the overall risk of developing depression 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 increase their time to 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.

## Methods

### Data Source

We performed our analysis with genetic data from the Finnish Institute for Health and Welfare (THL) Biobank that was collected as part of the examinations for the FINRISK and HEALTH surveys. The FINRISK surveys conducted health examination 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 or 2012.[26] The HEALTH survey included a sample of the Finnish population above the age of 30 collected in 2000 and 2011.[27] We linked these data to the Finnish national registers, which contain individual-level demographic and socioeconomic information on individuals permanently residing in Finland in 1987. The participants were followed up each calendar year. These data were subsequently linked 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 closed cohort of individuals residing in Finland from 1987 to 2019 between ages 25 and 80 years. The flowchart for sample selection can be found in Figure 1. 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 FINRISK 1992 and 1997 participants (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 1$^{st}$ or 2$^{nd}$ degree relatives of other participants based on a genetic relatedness indicator $\hat{\pi}$ of above 0.1875.[28] We furthermore excluded 127 individuals with interval censoring. The final analytic sample was 30,192 individuals.

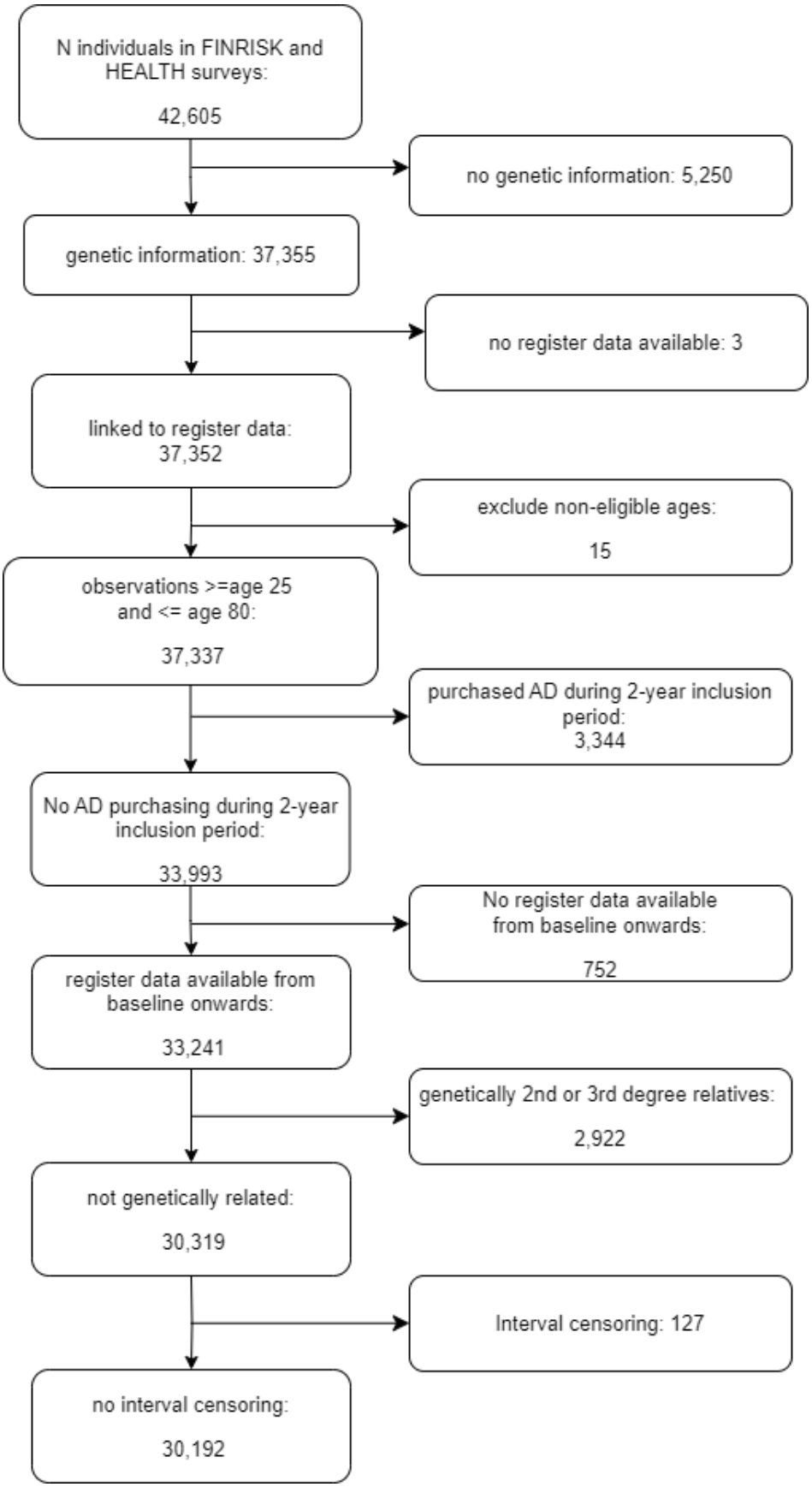
N individuals in FINRISK and HEALTH surveys:
42,605
no genetic information: 5,250
genetic information: 37,355
no register data available: 3
linked to register data:
37,352
exclude non-eligible ages:
15
observations >=age 25 and <= age 80:
37,337
purchased AD during 2-year inclusion period:
3,344
No AD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

*Figure 1 Flowchart for sample selection.*

### 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 PGSs that is based on a GWAS by Howard et al.[29] for a broad definition of depression (diagnosed MDD and self-reported depression). This GWAS 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. The 23and Me samples were excluded due to privacy policies for constructing the polygenic risk score.

The polygenic risk score was adjusted for linkage disequilibrium using SBayesR method, using summary statistics of Howard et al.[29] and linkage disequilibrium matrix provided by the authors of the method. These re-weighted scores were then summed to individual PGS using autosomal HapMap3 variants with MAF >0.01. We categorized the PGS into <=20$^{th}$ percentile, 21$^{st}$ to 79$^{th}$ percentile and >=80$^{th}$ 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 cohabitating); cohabitating; 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 marital 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 are easily interpretable and avoid the non-collapsibility and resulting selection bias of proportional hazard-based hazard ratios.[30,31] We assessed whether the Weibull, exponential, lognormal or log-logistic distribution was appropriate by plotting the predicted survival probability from each distribution against the crude survival probability (supplementary Figure 1).

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 1). 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[32] 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 a model without an interaction term (Model 3a) 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 at the 20$^{th}$ and 80$^{th}$ PGS percentile. For predictions, PCs of population structure were held constant at the mean and data/batch at Finpcga FINRISK for all models. Model 1 and 2 were averaged over age, sex and data/batch, Model 3 and 4 are additionally averaged over education. We performed subgroup analysis by gender.

*Table 1 Model specifications.*

| Model | Model specification |
|---|---|
| ***1*** | PGS + partnership status + age + sex + batch/sample + population structure |
| ***2*** | PGS * partnership status + age + sex + batch/sample + population structure |
| ***3*** | ***Model 1*** + education |
| ***3a*** | ***Model 2*** + education |
| ***4*** | PGS*(partnership status + age + sex + education) + partnership status*(age + sex + education) + batch/sample + population structure |

*Sensitivity Analysis*

As 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.[29]

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.[33] 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 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.

## Results

Sample characteristics at baseline can be found in Table 2. We followed 30,192 people (15771 females and 14421 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 80$^{th}$ PGS percentile purchased antidepressants during follow up, followed by 23.1% in the 21$^{st}$ to 79$^{th}$ percentile and 18.7% in the 20$^{th}$ percentile. Among partnership status groups, divorced participants most often purchased antidepressants, followed by single, widowed, cohabiting and married.

*Table 2 Sample Characteristics at baseline overall and for participants purchased antidepressants (AD) during the follow-up period.*

| | Overall | Purchased AD |
|---|---|---|
| | N | % |
| **Whole sample** | 30192 | 23.4 |
| **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 |
| | mean (SD) | |
| **Time to event or censoring** | 12.9 (6.1) | 7.1 (5.3) |
| **Age** | 50.2 (13.3) | 48.9 (12.8) |

**Error! Reference source not found.**Participants in the 80$^{th}$ PGS percentile or above had a higher cumulative incidence of antidepressant purchasing with a steeper slope across follow-up in all partnership status groups, compared to the 20$^{th}$ and 21$^{st}$ to 79$^{th}$ PGS percentiles (Figure 2). The cumulative incidence of antidepressant purchasing was lowest in the 20$^{th}$ PGS percentile for all

partnership status groups, though curves for the 20th and 21st to 79th percentile overlap in the cohabiting group.

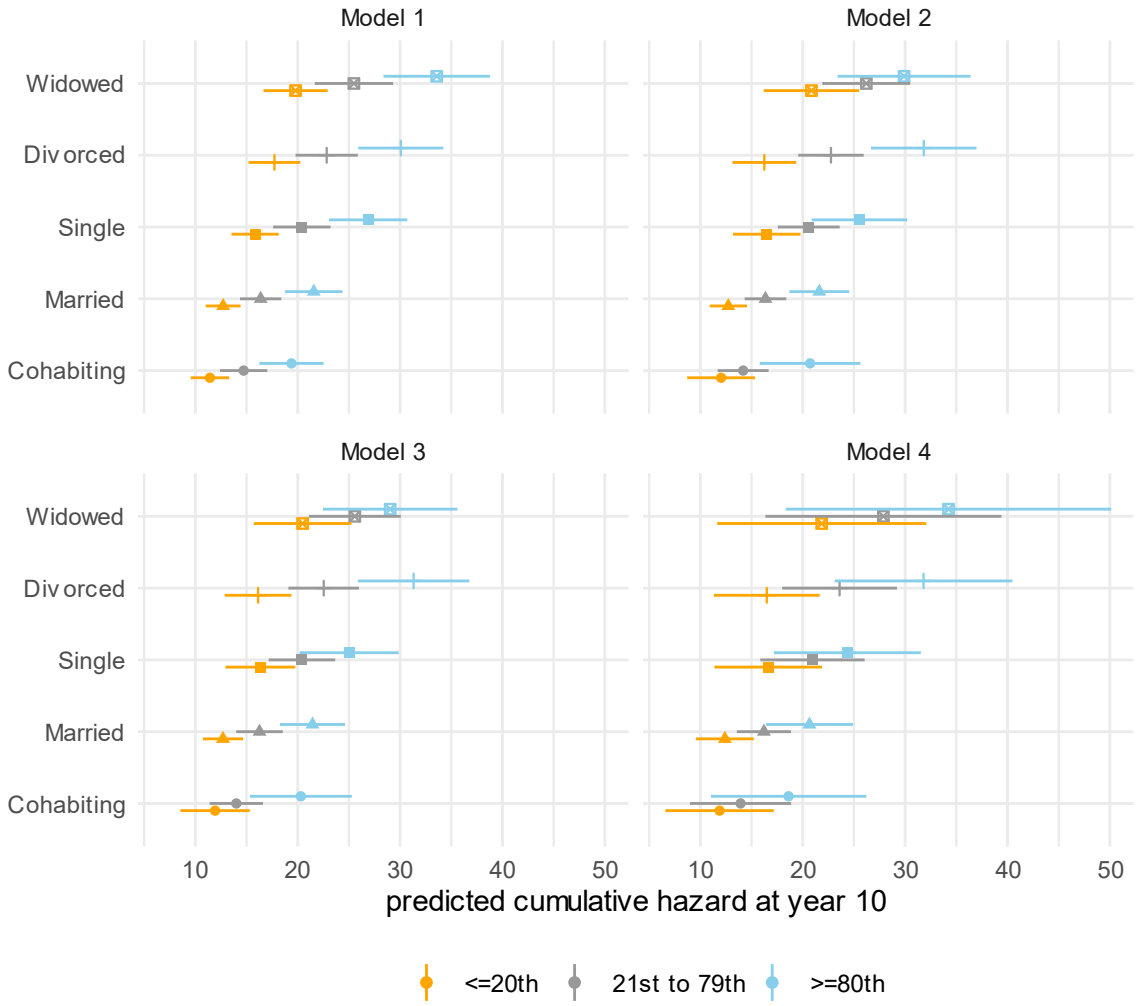


*Figure 3 Predicted cumulative hazard of antidepressant purchasing at follow-up year 10 for polygenic risk score percentiles and partnership status. Model 1 includes PGS, partnership status, age, sex, batch/sample and population structure PCs. Model 2 includes and interaction term between PGS and partnership status. Model 3: Model 2 with education, Model 4: Model 3 with Keller adjustment.*

Figure 4 shows the predicted cumulative hazard across follow-up for the 20th, 21th to 79th, and 80th PGS percentile by partnership status based on Model 3. 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 across follow-up time.

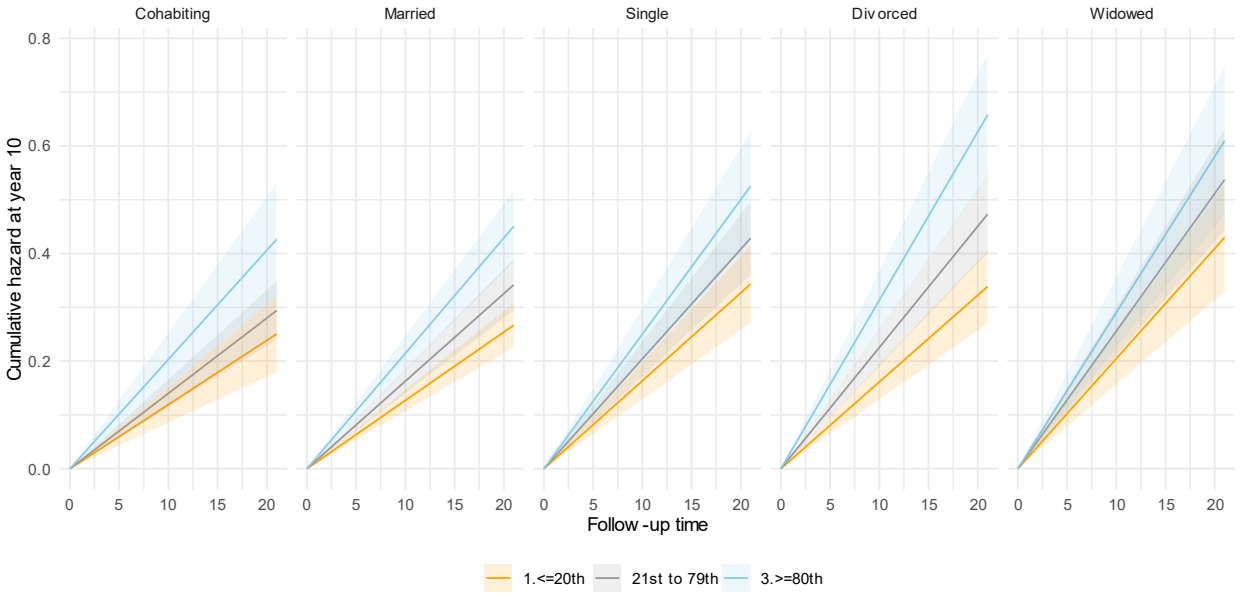


*Figure 4 Predicted cumulative hazard across follow-up time for PGS percentiles and partnership status. Predictions based on Model 3.*

## Sensitivity analysis

We observed marginal differences in the predicted cumulative hazard at year 10 across gender (supplementary Figure S.5 and Table S.3). Adjustment according to Keller[32] (Model 4) resulted in more uncertainty compared to the other model specification (Model 3).

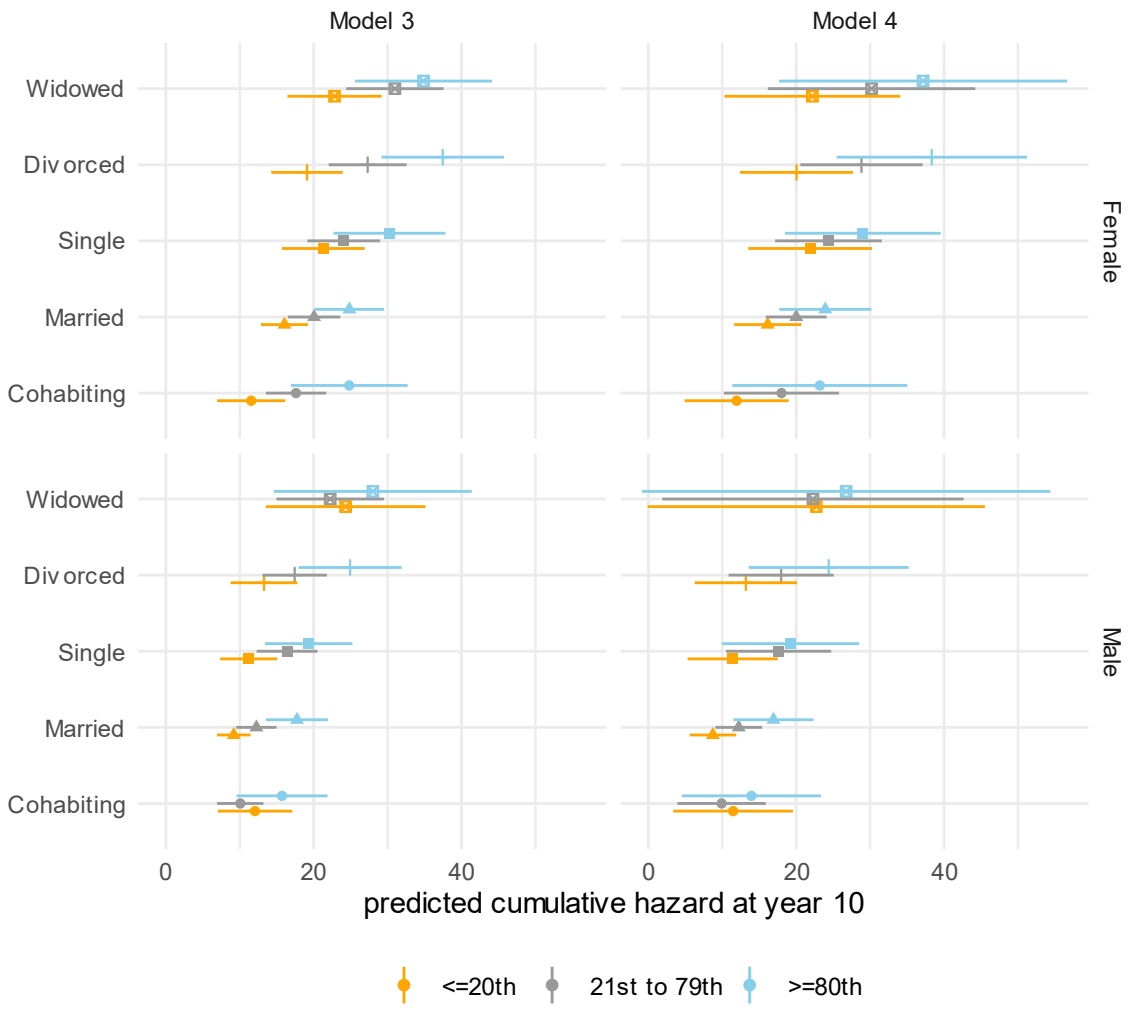


*Figure 5 Predicted cumulative hazard of antidepressant purchasing at follow-up year 10 for polygenic risk score percentiles and partnership status by sex. Model 3 includes interaction term between PGS and partnership status, age, batch/sample, education and population structure PCs. Model 4: Model 3 with Keller adjustment.*

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 at year 10 to the main analysis and the same conclusions as the main analysis (supplementary Figure S.2 and Table S.4).

In our sensitivity check for selection into marriage based on polygenic risk for depression, we found that one unit increase in PGS at the population level is associated with 7% increased odds of being divorced (supplementary Table S.4). This suggests a gene-environment correlation and inflated coefficient for the interaction between PGS and divorced.

## Discussion

Our study found that in Finnish adults between the age of 25 to 80 the predicted cumulative incidence of antidepressant purchasing was larger among participants in the 80$^{th}$ PGS percentile for MDD compared to the 20$^{th}$ PGS percentile among all partnership status groups. Among partnership status groups, widowed had the highest cumulative incidence of antidepressant purchasing, followed by divorced, single, married and cohabiting. We observed 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 across gender. Sensitivity analysis suggested that the results are robust to the choice of polygenic risk score for depression.

### Evaluation of Data and Methods

An advantage of our study was the use of the FINRISK and HEALTH surveys which can be linked with the Finish 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, a 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.[34] 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.[35] While the predictive power of a polygenic risk score might differ depending on which genetic variants are included[36], 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 2).

Antidepressant purchasing requires a medical practitioner's prescription but is not an MDD diagnosis. In Finland, primary care is responsible for the treatment of mild to moderate depression with the recommendation to prescribe antidepressants for acute depression,[37] resulting in about 50% of antidepressants being prescribed by doctors with no specialty.[38] Possibly as a result of

that, about one quarter of Finnish individuals who take antidepressants have no diagnosed mental disorder.[39] Hence, such biases may overestimate MDD 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[32], 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 effects that require more statistical power) and 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.

Our sensitivity analysis found that there is evidence for endogenous selection into divorce based on the PGS. This might introduce collider bias and could lead to an inflated interaction coefficient and overinterpretation of the magnitude of interaction.[33] 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 to disentangle the effects of mediation (introduced through endogenous selection) and interaction.

**Comparison with previous literature & interpretation of findings**

Our study found that partnership status and the PGS are independently associated with antidepressant purchasing. Our results were in line with Stringa et al.[25] who find no evidence for GxE between partner 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.[21] reported that the part of subjective well-being that is explained by genetics is smaller among married or cohabiting compared to single respondents. Beam et al[19] found similar results for married compared to divorced or 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 compared to research on the general population.[19,21] Second, twin models are based on different assumptions such as no assertive mating and the equal environment assumption which makes them less generalizable to the general population.[17] Lastly, heritability estimates from twin samples are higher than for SNP-based or PGS heritability.[7,8,17] With a larger heritability comes 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[40] which might affect the moderating effect of partnership status on the genetic susceptibility of depression. First, the association between marital status and mental health might depend on the perceived quality of the relationship or marriage. South et al.[41] 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 (SLE), and marriage or cohabitation may be defined as life change events.[42] SLEs were repeatedly examined as a potential moderator for the link between genetics and psychiatric disorders with mixed results depending on the sample and genetic variant(s) examined.[13,22,23] The association between experiencing a SLE and depression is strongest in the month that the SLE occurred and persists for up to 6 months.[43] 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 changed. Future research might benefit from combining structural and subjective indicators for social relationships and using a difference in difference type designs to assess the moderating effect of social relationships on the genetic susceptibility to depression.

## Conclusion

In line with previous evidence from observational studies, we found no evidence for partnership status moderating the genetic susceptibility to depression. In other words, we find no evidence that being married or cohabiting could partially offset the genetic susceptibility to depression.

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