Heterogenous associations of polygenic indices of 35 traits with mortality

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Abstract (247/250 words)

Background: Polygenic indices (PGIs) of various traits abound, but the knowledge remains limited on how they predict wide-ranging health indicators, such as mortality risk. We investigated the association between mortality and 35 different PGIs related to social, behavioural, psychological traits or typically non-fatal health conditions.

Methods: Individuals from population-representative genetically informed epidemiological surveys (Finrisk rounds 1992–2017, Health2000/2011, FinHealth 2017), linked to administrative registers, were followed to the end of 2019 (N: 40,097, 5948 deaths). Within-sibship analysis was complemented with dizygotic twins from Finnish twin study cohorts (N: 10,174, 2116 deaths). We fitted Cox regressions for 35 PGIs of various traits, adjusted for age, age^2, gender, data collection year and genetic principal components.

Results: PGIs most strongly predictive of all-cause mortality were ever smoking (HR=1.11, 95%CI 1.09;1.14 per 1 SD larger PGI), self-rated health (HR=0.90, 95%CI 0.88;0.93), educational attainment (HR=0.91, 95%CI 0.89;0.94), body mass index (HR=1.09, 95%CI 1.07;1.12), depressive symptoms (HR=1.07, 95%CI 1.04;1.10), and drinks per week (HR=1.06, 95%CI 1.04;1.09). Within-sibship estimates were roughly consistent with population analysis. Investigated PGIs were typically more predictive for external than for disease causes of death. The PGIs were more strongly associated to death occurring at younger ages, while among those who survived to age 80, the PGI-mortality associations were negligible.

Conclusions: PGIs related to the best-established phenotype health risk factors had the strongest associations with mortality. They offer moderate additional prediction even when their phenotype is measured. Within-sibship analysis indicated no evidence for inflation of PGI-mortality associations by population phenomena.

Keywords (3-10): Mortality, polygenic index, time-to-event analysis, within-sibship

Word count: ~3400 (too long)

Introduction

Due to decreased costs of genotyping and methodological advances, the possibility to predict individuals' complex traits from molecular genetic information has become increasingly available in large population samples and in health-care settings. The standard method for such prediction is to form polygenic indices (PGIs), constructed as an association-size weighted sum of single nucleotide polymorphisms (SNPs) associated with the phenotype of interest in an independent genome-wide association study (GWAS)[1–3]. One motivation for this enterprise has been to construct tools that may help clinical practice in disease risk prediction[4–6].

In addition to such a straightforward application in disease prediction, PGIs can possibly have utility for health risk assessment in a more indirect manner, as PGIs may have downstream importance in predicting health and functioning more widely beyond their immediate phenotypes, such as with regards to their overall mortality risk. Despite some earlier contributions[7–11], the knowledge on the extent that PGIs predict mortality is still scarce, and existing literature covers mostly disease or biomarker-related PGIs. However, it is largely unclear to what extent PGIs for social, psychological, and behavioural phenotypes or PGIs for typically non-fatal health conditions can help in mortality prediction. In addition, the research has increasingly shown the limitations of PGIs as black-box predictors, which may include – in addition to the usually-desired direct genetic signals – population-related phenomena due to geographical stratification of ancestries, dynastic or shared environmental effects in families and kins, as well as assortative mating. Within-sibship analysis designs may alleviate such limitations, exploiting the fact that the genetic differences between siblings are due to the random segregation at meiosis[1,12].

An individual's mortality risk is strongly associated with their gender, age and education[13,14], warranting an assessment on the potential heterogenous effects regarding them. It is also possible that social, psychological, and behaviour-related PGIs may matter disproportionately causes of death including accidents, suicides, violent and alcohol-related deaths, as such "external" mortality is conceptually closely connected to risky behaviour and alcohol consumption. A relevant question for their practical utility is also whether PGIs can bring additional information on predicting the risk of death also in cases when information of the measured phenotype is available.

In this study, we answer these gaps in knowledge by assessing the association between 35 different PGIs – mostly related to social, behavioural, psychological traits or typically non-fatal health conditions – and mortality using a population-representative sample of over 40,000 Finnish individuals with up to 25 years of mortality follow-up from national registers. We also investigate the extent of potential population-stratification and related biases by within-sibship analysis of over 10,000 siblings. Furthermore, we examine potential heterogeneous PGI-mortality associations by gender and education, as well as by

mortality occurring at different ages and between external and disease (other) causes of death. Finally, we investigate 6 PGIs that are most strongly associated with mortality (PGIs of ever smoking, self-rated health, body mass index [BMI], depressive symptoms, and drinks per week) and compare their estimates with corresponding phenotypes.

Methods

Study population

The main ("population") analysis sample consists of genetically informed population surveys FINRISK rounds 1992, 1997, 2002, 2007 and 2012, as well as Health 2000 and 2011 and FinHealth 2017[15–17]. The response rates of these data collections varied between 65 and 93%. 88% of the initial pooled sample had genotyped data available. The genetic data followed quality control and imputation procedures according to the Sequencing Initiative Suomi protocols[18,19]. These data were linked to administrative registers using pseudonymized personal identity codes, including socio-demographic and mortality information maintained by Statistics Finland. Other register-data used were obtained from the Care Register for Health Care maintained by the Finnish Institute of Health and welfare (THL) for hospital visits and medicine purchases from medicine reimbursement register by the Social Insurance Institution of Finland (Kela). This population analysis sample was complemented with within-sibship analysis. Individuals in sibling data were mainly dizygotic twins from Finnish twin cohorts: "old cohort" (born before 1959); FinnTwin12 (born 1974–1979) & Finntwin16 (1983–1987)[20]. These sibling data are complemented with individuals identified from the population sample as likely full siblings based on their genetic similarity (0.35<Identity by descent<0.80) and having age difference of less than 18 years. They were excluded from the population analysis to achieve non-overlapping samples.

The individuals were followed from (whichever latest) 1) the beginning of 1995, 2) the date of the data sample collection, 3) the month the respondent turned 25 years. The mortality follow-up ended on 31 December 2019 or at the time of the death. The analytic sample size was 40,097 individuals (564,885 person-years of follow-up) and 5948 deaths in the main analysis. In within-sibship analysis, we had 10,174 individuals (200,683 person-years of follow-up) in 5071 sibships and 2116 deaths.

Variables

The outcome was death that occurred during the follow up-period. We also disaggregated measure into external (accidents, violence, suicides, and alcohol-related causes of death; codes 41–53 in the national time series classification of Statistics Finland[21]) and disease (other codes) causes of death.

As the independent variables of main interest, we used 35 different PGIs in the Polygenic Index repository by Becker et al.[2]. We use all the PGIs that were available and tailored for the Finnish data, including indices for the following phenotypes: physical activity, attention deficit hyperactivity disorder (ADHD), adventurousness, age at first birth, asthma/eczema/rhinitis, asthma, alcohol misuse, body mass index (BMI), cannabis use, cigarettes per day, cognitive performance, depressive symptoms, drinks per week, educational attainment, ever smoker, extraversion, life satisfaction – family, life satisfaction – friend, hay fever (allergic rhinitis), height, highest math, age first menses, migraine, morning person, narcissism, near-sightedness, number of children ever born (women), neuroticism, openness, childhood reading, religious attendance, risk tolerance, self-rated health, self-rated math ability ,and subjective well-being. These scores were linkage disequilibrium-adjusted with LDpred[22], except for the educational attainment PGI, on which such adjustment was conducted by SBayesR[23]. For more details on the construction of PGIs, see[2]. The PGIs were standardized to have mean 0 and standard deviation (SD) 1.

We also measure 6 phenotypes that had strongest associations with mortality to compare their associations to corresponding PGIs. These are 1) body mass index (BMI), measured in clinical examination as kg/m^2. 2) Alcohol intake was measured as grams of pure ethanol consumed on average per week, based on survey report. 3) Depression was measured as number of depression indicators from different sources: a) self-reported depression in a survey, b) antidepressant purchases (ATC N06A, N06CA) or c) hospitalization due to depression (ICD10 codes F32–F39, except F323 & F333) as main or any other diagnosis. Medicine purchases and hospitalization was measured for a two-year period before the start of the follow-up (expect for medicine purchases the earliest possible measurement period is 1995–1997 due to data availability). The value of the variable was the sum of the number of the different measures of depression (ranging 0–3). 4) Education was measured based on registers as expected years after basic education to complete the most advanced degree of an individual: a) basic, b) secondary, c) lower tertiary, d) higher tertiary. 5) Smoking was based on self-reports and measured in three categories a) Never, b) Quitted at least 6 months ago, c) Yes. 6) Self rated health was evaluated in a five-point scale (1=worst; 5=best).

Methods

We estimated Cox proportional hazards regressions predicting mortality by the PGI in question. All the models were adjusted for gender, age at the start of the baseline, indicators for the data collection baseline year and the ten first principal components of the full (pruned) SNP matrix. See Supplementary table A for correlations between PGIs. The models were first estimated to the whole population sample. We compared these models to the corresponding within-sibship analysis, using the sibship identifier as the strata variable.

Next, we assessed for heterogenous effects by estimating the corresponding models among men and women separately, as well as in three educational groups. We also investigated possible age-related patterns by investigating age-specific deaths (25–64 years, 65–79-years, 80+ years), with corresponding follow-up periods. We also conducted an additional analysis by separating the outcome to external and disease causes of death.

Finally, we analysed the six PGIs with strongest association to mortality in more detail. Here we also measured corresponding phenotypes and fitted four types of models: Model 1 was adjusted for controls and each PGI/phenotype separately. Model 2 jointly adjusted corresponding PGI +phenotype. Model 3 adjusted for all PGIs or phenotypes (but not both simultaneously) and model 4 adjusted for both all six PGIs and phenotypes simultaneously. We also carried out an analysis stratified by whether the study participants had or had not the phenotypic risk factor.

Proportional hazards assumption of Cox models was evaluated with Schoenfeld residuals (see Supplementary table B)[24]. This investigation did not indicate substantial violation of proportional hazards on any of the investigated PGIs as all their residual correlations were between -0.022 and 0.026 in the population sample. The correlations with investigated phenotypes were slightly higher, with absolute values of residual correlations less than 0.08 in all cases.

The software used for producing genetic variables was PLINK v. 1.9/2.0. The statistical analysis was conducted with Stata v16.

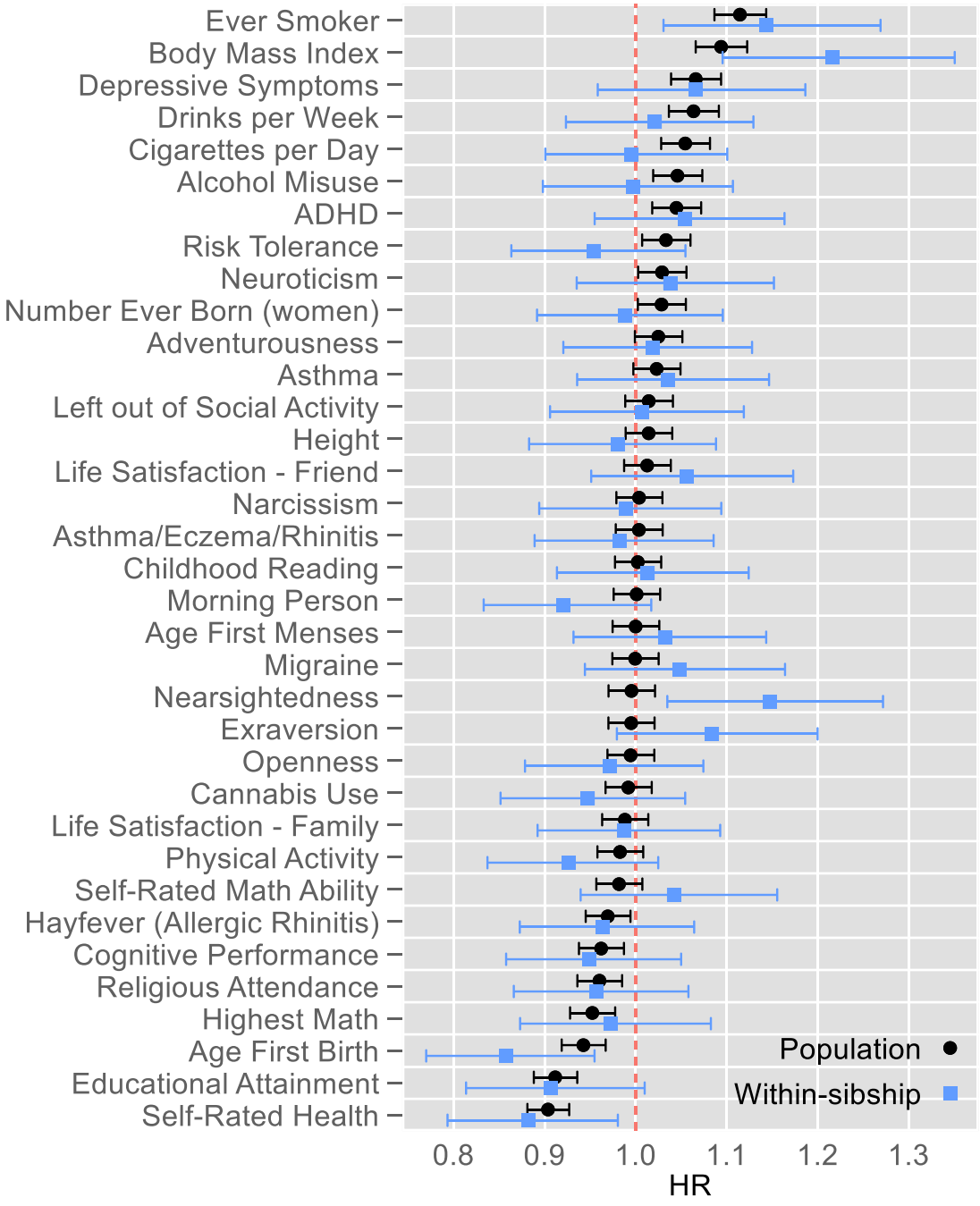
Results

Figure 1 the association between analysed PGIs and all-cause mortality. On the population analysis, following PGIs predicted mortality the strongest: ever smoking (hazard ratio [HR] per 1 SD larger PGI =1.11, 95 per cent confidence interval [95%CI]= 1.09;1.14), self-rated health (HR=0.90, 95%CI 0.88;0.93), educational attainment (HR=0.91, 95%CI 0.89;9.94), BMI (HR=1.09, 95%CI 1.07;1.12), depressive symptoms (HR=1.07, 95%CI 1.04;1.09), drinks per week (HR=1.06, 95%CI 1.04;1.09) and age at first birth (HR=0.94, 95%CI 0.92;0.97). Most PGIs had negligible associations with the mortality hazard, as 18 out of 35 studied PGI had HRs between 0.98 and 1.02.

The within-sibship estimates presented in Figure 1 were estimated less precisely than population estimates, as evidenced by their wider 95% CIs but the within-sibship estimates were overall not weaker than population estimates. Although confidence intervals overlapped with regards to every individual PGI, on average within-sibship analysis had even marginally larger associations than in population analysis (inverse-variance-weighted mean absolute log HR was 0.021, 95%CI 0.003;0.039 larger in within-sibship than population analyses). In within-sibship analysis, PGI of BMI had the strongest association

with mortality (HR=1.22, 95%CI 1.10;1.35), followed by age at first birth (HR=0.86, 95%CI 0.77;0.95), ever smoking (HR=1.14, 95%CI 1.03;1.27), extraversion (HR=1.14, 95%CI 1.03;1.27) and self-rated health (HR=0.88, 95%CI 0.79;0.98).

Figure 1 HRs of PGIs in predicting all-cause mortality. Population and within-sibship estimates.



Note: Estimates from Cox proportional hazards models adjusted for time of birth, age at the start of the follow-up, gender and 10 first principal components of the genome. Capped bars are 95% confidence intervals. For a table of corresponding estimates, see Supplementary table C.

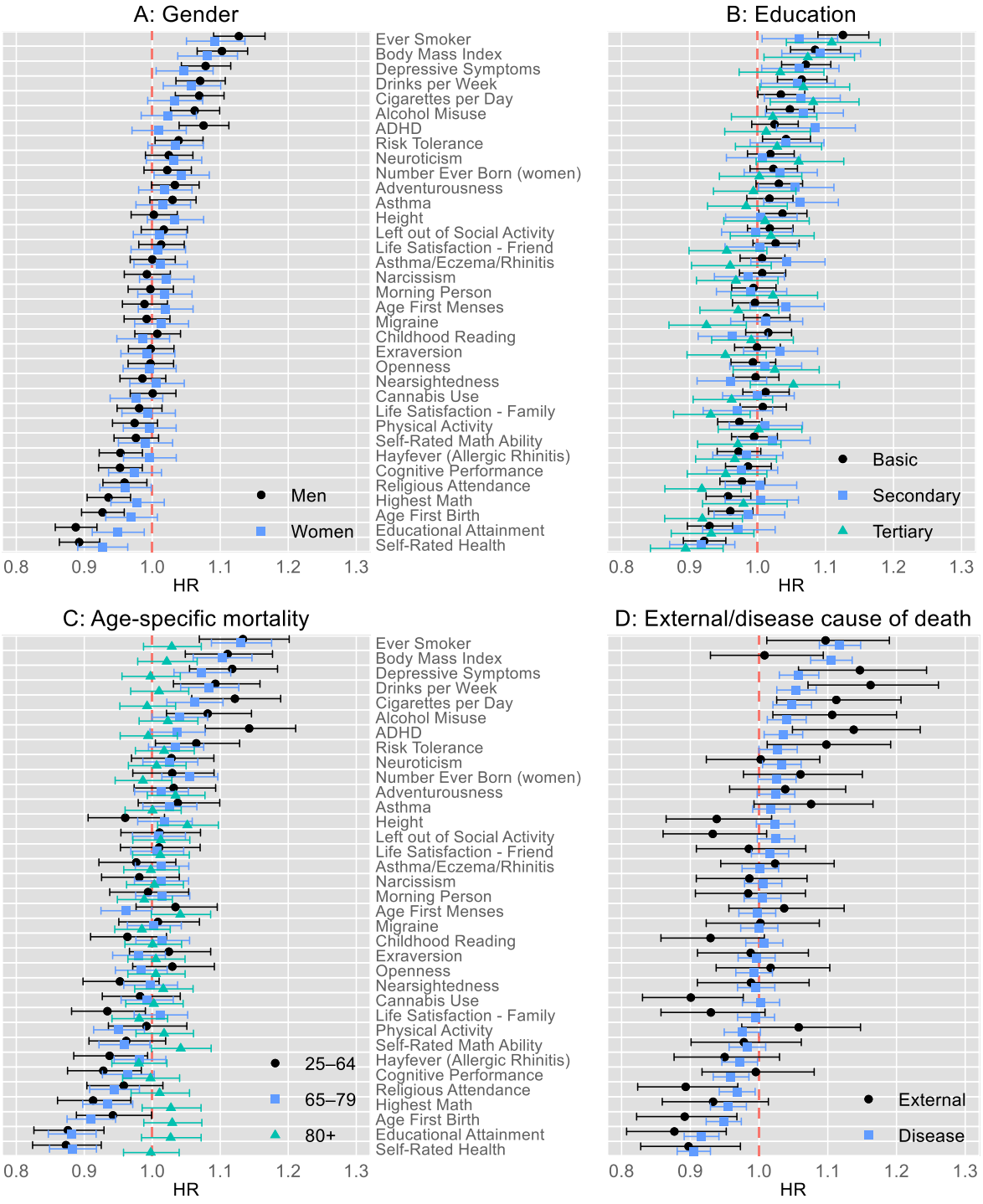
Figure 2 presents potential heterogenous or cause-of-death differences in PGI-mortality associations. Panel A displays HRs of mortality estimated from gender-stratified models. Overall, men had slightly stronger PGI-mortality associations across the board (inverse-variance-weighted mean absolute log HR was 0.013, 95%CI 0.004;0.021 larger among men). However, the gender differences were overall modest with regards of all PGIs, with largest gender difference for PGI of ADHD (HR=1.08 95%CI 1.04;1.11 among men; HR=1.01 95%CI 0.97;1.05 among women; p=0.017 for difference).

Panel B of Figure 2 presents the HRs of different PGIs estimated separately in three different educational groups, indicating no evidence for heterogeneous associations by educational groups.

Panel C of Figure 2 presents the HRs of different PGIs estimated in stratified models by the age of death (25–64, 65–79 and 80 years or older). The PGIs were more predictive of the death hazard at younger age groups. The difference between 25–64 and 65–79 age deaths was small, with biggest difference for PGI of ADHD (HR=1.14 95%CI 1.08;1.21 for 25–64-year-olds; HR=1.04 95%CI 1.00;1.08 for 65–79-year-olds; p=0.006 for difference). In the mortality of oldest age group (80+), in turn, investigated PGIs predicted deaths only negligibly.

Panel D of Figure 2 displays the HRs disaggregated in external (accidents, violent, suicide and alcohol related deaths) and disease causes of death. Overall, PGIs had stronger associations in external than in the other causes of death. For external causes, strongest association were observed for PGI for drinks per week (HR=1.17, 95%CI 1.07;1.26), depressive symptoms (HR=1.15, 95%CI 1.06;1.25) and ADHD (HR=1.14, 95%CI 1.05;1.23). 12/35 of the studied PGIs had HRs >1.1 (drinks per week, depressive symptoms, ADHD, cognitive performance, alcohol misuse, ever smoker) or <0.9 (cannabis use, self-rated health, religious attendance, age of first birth and educational attainment) per 1 SD difference in PGI, whereas the corresponding number was 2/35 (for ever smoking and body mass index) for other causes of death. Several behaviour-related PGIs showed associations in external causes of death, whereas HRs of disease causes of death followed similar patterns as all-cause mortality, which was expected, as the disease causes constituted 90% of all observed deaths.

Figure 2. HRs of PGIs in predicting all-cause mortality. Estimates by gender (Panel A), educational groups (Panel B), age specific mortality/follow-up periods (Panel C) and external/other cause of death (Panel D).



Note: Estimates from Cox proportional hazards models adjusted for time of birth, age at the start of the follow-up, gender and 10 first principal components of the genome. Capped bars are 95% confidence intervals. External causes of death included accidents, suicides, violent, and alcohol related deaths. For a table of corresponding estimates, see Supplementary table D.

Table 1. Hazard ratios from Cox models predicting mortality by six most predictive polygenic indices and corresponding risk factors (N: 37,548 individuals; 5407 deaths)

	Model 1a-1l			Model 2a-2f			Model 3a& 3B			Model 4		
	HR	95%lci	95%uci	HR	95%lci	95%uci	HR	95%lci	95%uci	HR	95%lci	95%uci
Smoking	1.41	1.37	1.46	1.40	1.36	1.44	1.35	1.31	1.39	1.33	1.29	1.38
PGI-ever smoking	1.12	1.09	1.15	1.06	1.04	1.09	1.07	1.04	1.10	1.04	1.01	1.07
BMI	1.07	1.04	1.10	1.04	1.01	1.07	1.02	0.99	1.05	1.00	0.97	1.03
PGI-BMI	1.09	1.06	1.12	1.08	1.05	1.11	1.05	1.02	1.08	1.03	1.00	1.06
Depression indicators	1.16	1.13	1.19	1.16	1.13	1.19	1.06	1.03	1.09	1.06	1.03	1.09
PGI-depressive symptoms	1.07	1.04	1.10	1.05	1.03	1.08	1.02	0.99	1.05	1.00	0.97	1.03
Alcohol intake	1.16	1.13	1.19	1.16	1.13	1.19	1.12	1.09	1.15	1.11	1.08	1.14
PGI-drinks per week	1.06	1.03	1.09	1.05	1.02	1.08	1.05	1.02	1.08	1.03	1.00	1.06
Education years	0.86	0.83	0.88	0.87	0.84	0.90	0.90	0.88	0.93	0.91	0.88	0.94
PGI-educational attainment	0.91	0.89	0.94	0.94	0.92	0.97	0.96	0.93	0.99	1.02	0.99	1.05
Self-rated health	0.74	0.72	0.76	0.75	0.73	0.77	0.78	0.76	0.80	0.78	0.76	0.80
PGI-self rated health	0.90	0.88	0.93	0.94	0.91	0.97	0.95	0.92	0.99	0.97	0.94	1.01

All presented variables standardized to have SD=1. For corresponding models with categorical phenotypes, see Supplementary table E.
All models adjusted for baseline covariates: age at the baseline continuous + squared), gender, indicators of the baseline data collection and ten first principal components of the genome..
Models 1: Baseline covariates + phenotype/PGI in question.
Models 2: PGI and corresponding phenotype mutually adjusted.
Model 3a: Phenotypes mutually adjusted, Model 3b: PGIs mutually adjusted
Model 4: Full model

Table 1 analyses a selection of the PGIs of the previous analyses with the strongest associations on mortality (ever smoking, self-rated health, educational attainment, BMI, depressive symptoms and drinks per week) and analyses the conjointly with related phenotypes (smoking, self-rated health, years of education, BMI, number of depression indicators, and alcohol intake per week). Model 1 presents HRs of each variable adjusted only for baseline covariates. Except for BMI, a one SD increase of the phenotype has stronger effect than their respective PGIs. The HR of the phenotype is often from one third to one half more extreme (distant from 1), and even larger difference was observed for smoking and self-rated health. Model 2 adjusts a phenotype and their respective PGI simultaneously. Adjusting for the respective PGIs decrease the HRs of phenotypes only slightly, whereas for PGIs this attenuation was around one third on average. Model 3a adjusts all investigated phenotypes and 3b all investigated PGIs simultaneously. This adjustment strongly attenuates both depression indicators and the PGI of depressive symptoms most substantially. Finally, model 4 adjusts all phenotypes and PGIs

simultaneously. In this final model, smoking (HR=1.33, 95%CI 1.29;1.38) and self-rated health (HR=0.78, 95%CI 0.76;0.80) were the strongest predictors of mortality, followed by alcohol intake (HR=1.11, 95%CI 1.08;1.14), and years of education (HR=0.91, 95%CI 0.88;0.94). In model 4, PGIs had only modest independent associations, strongest was PGI of smoking (HR=1.04, 95%CI 1.01;1.07), PGI of BMI (HR=1.03, 95%CI 1.00;1.06) and PGI of drinks per week (HR=1.03, 95%CI 1.00;1.06). Supplementary table E presents corresponding analyses of Table 1 in the main text, but with phenotype measured categorically. This analysis indicates curvilinear morality patterns for BMI and alcohol intake. This suggests that their HRs in Table 1 should be interpreted with caution. However, as the main focus of this study, the HRs of PGIs where largely unaffected by the change of the measurement of PGIs.

Table 2. Hazard ratios from Cox models predicting mortality with selected PGIs in the presence or absence of a related risk factors

	Without risk factor			With risk factor		
	HR	95%lci	95%uci	HR	95%lci	95%uci
PGI-ever smoking	1.07	1.03	1.11	1.08	1.05	1.12
PGI-BMI	1.13	1.07	1.19	1.09	1.06	1.13
PGI-depressive symptoms	1.05	1.02	1.08	1.06	1.00	1.12
PGI-drinks per week	1.09	1.03	1.15	1.07	1.04	1.10
PGI-educational attainment	0.87	0.75	1.01	0.93	0.90	0.95
PGI-self rated health	0.88	0.80	0.97	0.91	0.89	0.94

Without risk factor categories consists of: Never smokers (N:21,189), BMI 18.5-25 (N:15,092), no depression indicators (N:31,089), Non-drinkers (N:5498), higher-tertiary-degree holders (N: 4765), with best self-rated health (5-point scale, N:7566)

"With risk factor" are those in population sample with valid information on the risk factor in question excluding "without risk factor" -category.

All models adjusted for age at the baseline continuous + squared), gender, indicators of the baseline data collection and ten first principal components of the genome.

Table 2 investigates the associations between these 6 PGIs (ever smoking, self-rated health, educational attainment, BMI, depressive symptoms, and drinks per week) and mortality stratified by whether an individual was lacking the phenotype risk factor in question (non-smokers, best self-rated health category, higher tertiary education, BMI 18.5–25, no depression indicators, non-drinkers). We did not observe evidence for substantial difference in PGI-mortality HR between individuals with and without these risk factors in their corresponding phenotype. Furthermore, the only PGI that showed consistent attenuation in their HRs compared to the analysis on the whole sample (presented e.g. in Table 1 and Figure 1) was

PGI of ever smoking (HR=1.07, 95%CI 1.03;1.11 for never smokers, HR=1.08, 95%CI 1.05;1.12 for others, c.f. HR=1.12, 95%CI 1.09;1.15 for unstratified population analysis).

Discussion

We investigated the association between 35 different PGIs – mostly related to social, behavioural, psychological traits or traits of typically non-fatal health conditions – and mortality using a population-representative register-linked sample from Finland. PGIs most strongly associated to mortality were typically related to the best-established phenotypic mortality risk factors, including smoking, self-rated health, body mass index, education and alcohol consumption[25–27]. Although the majority of the investigated PGIs had negligible associations with the risk of death, the strongest associations observed were about a 10% difference in the risk of mortality for 1 SD difference in PGI. Given the severity of the outcome, these associations cannot be disregarded as trivial, particularly when considering individuals with particularly high or low PGIs. Moreover, our within-sibship analysis did not indicate that these PGI-mortality associations were systematically inflated due to population stratification or related biases. Limited previous literature exists overall on PGI-mortality associations, particularly for other than disease or biomarker related PGIs. However, the associations of PGIs of smoking, alcohol consumption, depression and BMI were roughly comparable or moderately stronger that what was observed in a previous study on the UK Biobank for PGIs unadjusted for each other[10] and in U.S. based Health and Retirement Study for mutually adjusted PGIs[9].

The investigated PGIs were slightly more predictive of mortality among men than women across the board, which aligns with gender differences observed for many social-level (phenotypic) mortality risk factors such as socioeconomic position and marital status[28–30], but similar excess risk among men is not consistently observed on more physiologically proximate/ behavioural mortality risk factors such as obesity, alcohol use and smoking[31–33]. In turn, we did not observe differences in PGI-mortality associations between educational groups. The PGIs were more predictive of death at younger ages, whereas among those who survived to age 80, PGIs made hardly any difference in morality risk. This contrasts previous study which aimed to directly identify SNPs associated with mortality (instead of PGIs of other phenotypes as done here) that found stronger HRs at older age groups[7]. Our findings echo "age as a leveller" age-pattern of associations often observed with regards to phenotypic indicators of socioeconomic position[13], although typically in milder extent. A possible explanation may lie in the increasing importance of acute mortality-risk enhancing factors towards the end of life, including emerging illness and biological ageing, that trump more distant and indirect mechanisms[13,34]. Such age–specific heterogeneity has also methodological implications, as it warrants caution in the extrapolation of

findings from studies that assess PGI-mortality association among samples of (mostly) older individuals. These results may not generalize to the overall population due to potential collider bias[35,36].

In general, PGIs were more strongly predictive of external than disease causes of death, and this was particularly evident for many psychological, behavioural and alcohol-use related PGIs, including drinks per week, ADHD, depressive symptoms, religious attendance, and risk tolerance. Only the PGI of BMI showed clearly stronger association with disease causes. It is worth noting that despite that alcohol-related deaths were included in external causes, smoking-related PGIs predicted both external and disease mortality in roughly consistent manner and PGI of cannabis use had even a negative association with external mortality. This suggest that despite a substantial shared genetic aetiology between different addictions[37,38], the genetic architecture between the use of different substances also differs importantly from the perspective of mortality risk.

Overall, among the PGIs most predictive of mortality, their associations tend to be roughly one third of the strength of the respective phenotypes when mutually adjusted. The stronger association of the actual phenotype is not surprising, but the observation, together with that PGIs were predictive also among those who lack the phenotypic risk factor, nevertheless imply that PGIs provide additional information relevant to the risk of death even when the phenotype measure is available. The potential advantage of PGIs in research and health care relative to phenotype is that they need to be measured only once, whereas for many phenotypes most relevant information would require extensive longitudinal information. This is particularly relevant for phenotypes related to a specific points of life course, e.g. on health-related factors typically manifesting on older age. This suggests that the independent association of PGIs might be stronger if we had even longer mortality follow-up. PGIs also avoid some forms of potential measurement error, such as those related to self-reporting.

The strengths of this study included population-representative data with high response rates linked with a long register-based-follow-up with minimal attrition-related biases. In turn, PGIs have known limitations, as they capture the genetic liability incompletely, are agnostic regards to the specific biological mechanisms and may also capture environmental signals[1]. Within-sibship analysis allowed to evaluate and mitigate population stratification and other related biases in the analyses. However, the within-sibship estimates suffer from lower statistical precision (evidenced by their wider 95% CIs) and are more sensitive to measurement error than corresponding population estimates[39]. In addition, the comparability of the PGIs is limited by differences in the GWASes that underlie them, e.g. in their sample sizes and phenotype measurement quality. Finally, the Schoenfeld residual correlations suggested some violation of the proportional hazards assumption in studied phenotypes. These phenotypes were however, not in the main focus here, and none of the PGIs showed evidence for such violation.

To conclude, PGIs related to the best-established phenotype health risk factors had the strongest associations with mortality. Particularly for deaths occurring at younger ages, PGIs offer information on mortality risk, even when related phenotype is available, and within-sibship analysis suggests that such associations appear not systematically inflated by population phenomena.

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