Joint associations of depression, genetic susceptibility and the area of residence for coronary heart disease incidence

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ABSTRACT

Background: Depression is a risk factor for coronary heart disease (CHD), but less is known whether genetic susceptibility to CHD or regional level social indicators modify this association.

Methods: Risk factors of CHD including a polygenic risk score (PRS) were measured for 19,999 individuals residing in Finland in 1997, 2002, 2007 and 2012 (response rates 60%–75%). During the register-based follow-up until 2015, there were 1381 fatal and non-fatal incident CHD events. Unemployment rate, degree of urbanisation and crime rate of the municipality of residence were used as regional level social indicators. Hazard ratios (HR) were calculated using register based antidepressant purchases as a non-reversible time-dependent co-variate.

Results: Those having depression and in the highest quartile of PRS had somewhat higher CHD risk than predicted only by the main effects of depression and PRS (HR for interaction 1.53 95% CI 0.95–2.45). Depression was moderately associated with CHD in high crime (HR=1.51 95% CI 1.20–1.90) and weakly in low crime regions (HR=1.07 95% CI 0.86–1.33; p-value of interaction=0.087). Otherwise, we did not found evidence for interactions.

Conclusions: Those having both depression and high genetic susceptibility need a special attention in health care for CHD.

What is already known on this subject?

1) Depression increases the risk of coronary heart disease.

2) Genetic susceptibility and socio-economic factors are associated with the risk coronary heart disease.

What this study adds?

1) Depression and high genetic risk showed suggestive interaction for coronary heart disease whereas there was only weak evidence for interaction between area-level
Social indicators and depression.

2) Persons with depression and high genetic susceptibility are in increased risk for coronary heart disease and thus needs special attention in health care.

Coronary heart disease (CHD) is globally the leading cause of death (1). Genome-wide association studies have shown the role of genetic susceptibility in CHD risk (2) supported also by familial clustering of CHD risk (3). In addition, both individual and regional level socioeconomic factors are found to be associated with the risk of CHD (4). However, a component of the CHD risk could be related to mental health, since depression may increase the risk of CHD (5). The physiological mechanisms behind this association are not yet known, but previous studies have shown that the polygenic risk score (PRS) for depression predicts CVD risk suggesting that there may be a shared genetic background for these diseases (6,7). This is further supported by results that loneliness and severe mental health disorders share several loci with CHD risk factors (8). Previous studies have given only little evidence on the multiplicative interactions of genetic risk with lifestyle (9) or social factors when predicting CHD risk (10). However, the fact that only a fraction of those experiencing psychological distress will eventually develop CHD suggests that there may be factors protecting from the harmful effects of psychological distress. Studies analysing whether genetic or environmental factors modify the association between depression and CHD risk are few. As direct evidence on how genetic or social factors modify the effect of depression on incident CHD events is lacking, we analysed this question in a large prospective cohort study.

Data and methods

We used the national FINRISK surveys conducted in 1997, 2002, 2007 and 2012 in men and women aged 25–75 years residing in Finland (11). The participation rates varied between 60% and 75% with higher participation rates in the earlier surveys. All surveys included physical examinations where height, weight, and systolic and diastolic blood pressure were measured. Total and HDL cholesterol were analysed from blood samples. Further, the participants reported their smoking status, alcohol use and education in a self-administrated questionnaire. Diabetes status was

based on the information from National Hospital Discharge Register (ICD-10 codes E10–E14), National Register of Reimbursed Medication (ATC code A10) and National Register of Special Reimbursement Right for Medication (code 103). These variables were used as co-variates in the analyses (see Supplementary table 1 for descriptive statistics). Depression status was measured as antidepressant purchases based on National Register of Reimbursed Medication (ATC code N06A). Non-fatal incident CHD events were based on Hospital Discharge Register (ICD-10 codes I20.0, I21–I22) and the fatal events on National Mortality Register (ICD-10 codes I20–I25, I46, R96 and R98). All registers cover the entire Finnish population and are linked to the sampled population using unique personal identification numbers. The PRS of CHD was based on 6,412,950 genetic variants using 20,179 individuals (12); in order to avoid overfitting, the PRS was generated independently of the FINRISK study cohorts. Information on urbanization level, crime rate and unemployment rate of the municipality of residence at the baseline were based on the public database of the Statistics Finland. Municipalities were categorized into high and low with median level as the cut-off. Altogether, we had information on 19,999 participants. During the follow-up of 249,470 person years until the end of 2015, 3779 participants used depression medications and 1381 had fatal or non-fatal CHD. Ethical approval has been obtained according to required procedures over the study years.

Hazard ratios (HR) with 95% confidence intervals (CI) were calculated by Cox proportional hazards models using incident CHD events as the outcome variable. Depression status was used as a non-reversible time-dependent co-variate with a 1-year lag to avoid the effect of CHD symptoms on depression. All other co-variates were measured at the baseline. We calculated interactions both by using PRS quartiles and when comparing the bottom and top 12.5% shares of PRS to test whether the risk is different in the extremes of PRS distribution. Further, we calculated the odds ratios (OR) of CHD-PRS for predicting depression status. Population stratification was adjusted for 10 principal

components of the genome. The modelling was conducted using Stata statistical package, version 14.2. (College Station, TX: StataCorp LP).

Results

Table 1 presents the HRs of CHD by the quartiles of PRS and depression status. PRS showed a clear gradient so that higher genetic risk was associated with higher risk of CHD, and depressed persons also had higher risk of CHD (Model 0). Adjusting the models for metabolic and behavioural risk factors of CHD had virtually no effect on the HRs (Model 1). Further, when we adjusted the models for education (Model 2) and mutually for PRS and depression status (Model 3), the HRs of CHD did not change for PRS or depression. Generally, there was only weak evidence for the interaction between PRS and depression status (p=0.217). However, those in the highest quartile of PRS and depression had somewhat higher CHD risk than predicted only by the main effects of depression and PRS (HR for interaction 1.53 95% CI 0.95-2.45). PRS was weakly associated with depression status: ORs 1.00 (lowest category); 1.04 95% CI 0.95-1.16; 1.01 95% CI 0.91-1.12 and 1.08 95% CI 0.98-1.20 (highest category).

We then analysed the associations of CHD risk with PRS and depression status by regional level indicators. Degree of urbanization (Supplementary table 2) or unemployment rate (Supplementary table 3) did not show any interaction with PRS (p=0.915 and p=0.303, respectively) or with depression status (p=0.421 and p=0.137, respectively). When using crime rate as the regional level indicator, we found that PRS did not show the region-level interaction (p=0.782). Depression status was moderately associated with incident CHD events in the municipalities with high crime rate (HR=1.51 95% CI 1.20–1.90) and weakly in the municipalities with low crime rate (HR=1.07 95% CI 0.86–1.33, p value of interaction=0.087)). Adjusting the results for CHD metabolic and

behavioural risk factors, education and PRS did not change the HRs. Degree of urbanisation (online supplemental table 2) or unemployment rate (online supplemental table 3) did not show any interaction with PRS (p=0.915 and p=0.303, respectively) or with depression status (p=0.421 and p=0.137, respectively). Interactions only for those with low versus high genetic risk (the top and bottom 12.5% shares of PRS) were not observed (p≥0.123).

Discussion

In this large and representative prospective cohort study with 1381 CHD events during the follow-up, we found, expectedly, both the PRS and depression status were strong predictors of incident CHD events. Our results also gave some suggestive evidence that depression may increase CHD risk in those having the highest genetic risk. Previous studies have not found multiplicative interaction between genetic susceptibility and lifestyle factors (9) or socio-economic factors when predicting CHD incidence (10). However, there is some evidence for gene-environment interactions for CHD risk factors, especially that obesogenic environment can reinforce the effect of genes predisposing to obesity (13,14). The gene-environment interactions for CHD are complex, and thus further studies with large sample sizes are needed to demonstrate whether there are factors modifying the genetic risk of CHD.

When considering the regional level social indicators, we found that depression was a slightly stronger predictor of CHD if the level of crime in municipality was high. Regional level unemployment or urbanization did not modify the effect of depression or genetic susceptibility of CHD risk. Further, we found that the PRS of CHD was only weakly associated with depression and the mutual adjustment of PRS and depression did not decrease the effect sizes of either of them.

This result is against a previous results that psychological distress and CHD would partly share the same genetic background (8).

Our study has several strengths as well as limitations. Our register-based information not only on incident CHD events but also depression status based on medication used as a time dependent covariate are not prone to reporting bias or selective non-response during the follow-up. However, antidepressants are also used for purposes other than clinically defined depression, such as pain or insomnia, which may attenuate the found associations (15). Further, there can be differences in the access to health care especially because those who are not employed are not eligible to occupational health care. This may have led to underdiagnoses of depression among those in lower socio-economic positions. Our cohort has good response rates thus well representing the Finnish population. The number of incident CHD events was large enough to detect all main effects, but it may be underpowered to observe small interaction effects between PRS and depression status. A limitation is also that the regional level social indicators are based on the municipality level data. However, there can be considerable spatial variation within municipalities in the social indicators studied.

In conclusion, depression is a risk factor of CHD largely independently of area level characteristics. However, those with both depression and high genetic susceptibility are in especially high risk to develop CHD and thus need special attention in health care.

Competing interests

VS reports personal fees from Novo Nordisk and Sanofi for consulting and grants from Bayer LDT outside this work.

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Table 1. Hazard ratios of CHD events for quartiles of PRS and depression status.

	Model 0		Model 1		Model 2		Model 3	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
PRS								
1 Low	1.00		1.00		1.00		1.00	
2	1.25	(1.06-1.48)	1.21	(1.02-1.43)	1.21	(1.02-1.43)	1.21	(1.02-1.43)
3	1.49	(1.27-1.75)	1.43	(1.21-1.67)	1.42	(1.21-1.67)	1.42	(1.21-1.67)
4 High	2.06	(1.77-2.40)	1.96	(1.68-2.29)	1.96	(1.68-2.29)	1.97	(1.69-2.29)
Depression								
No	1.00		1.00		1.00		1.00	
Yes	1.24	(1.06-1.45)	1.23	(1.05-1.43)	1.23	(1.05-1.44)	1.23	(1.05-1.44)

Model 0, 1 and 2: Separate models for PRS and depression status; All models adjusted for age, sex, calendar year, 10 principal components and genotyping batch

Model 1: Model 0 additionally adjusted for body mass index, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, prevalent diabetes, smoking status and alcohol use; Model 2: Model 1 additionally adjusted for education; Model 3: PRS and depression mutually adjusted

PRS*depression interaction $\chi^2(3)=1.45$, p=0.217; interaction terms for those having diagnosed depression (the main effects of PRS and depression adjusted in the model): 1.13 95% CI 0.67-1.92 (2. category); 1.11 95% CI 0.66-1.85 (3. category); 1.53 95% CI 0.95-2.45 (highest category)

PRS (top versus bottom 12.5% share)*depression interaction $\chi^2(1)=0.24$, p=0.622

Table 2. Hazard ratios of CHD event for quartiles of PRS and depression status by crime rate.

	Model 0		Model 1		Model 2		Model 3	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Crime rate								
Low								
PRS								
1 Low	1.00		1.00		1.00		1.00	
2	1.17	(0.94-1.45)	1.13	(0.91-1.40)	1.12	(0.91-1.39)	1.13	(0.91-1.40)
3	1.40	(1.14-1.72)	1.31	(1.06-1.60)	1.30	(1.06-1.60)	1.30	(1.06-1.60)
4 High	1.96	(1.61-2.38)	1.87	(1.54-2.28)	1.87	(1.54-2.27)	1.87	(1.54-2.27)
Depression								
No	1.00		1.00		1.00		1.00	
Yes	1.07	(0.86-1.33)	1.06	(0.85-1.32)	1.06	(0.85-1.32)	1.06	(0.85-1.32)
Crime rate								
High								
PRS								
1 Low	1.00		1.00		1.00		1.00	
2	1.39	(1.06-1.82)	1.36	(1.04-1.78)	1.35	(1.03-1.77)	1.36	(1.04-1.77)
3	1.65	(1.27-2.14)	1.63	(1.26-2.12)	1.62	(1.25-2.11)	1.64	(1.26-2.13)
4 High	2.20	(1.71-2.82)	2.06	(1.60-2.65)	2.09	(1.62-2.69)	2.09	(1.62-2.68)
Depression								
No	1.00		1.00		1.00		1.00	
Yes	1.51	(1.20-1.90)	1.49	(1.18-1.87)	1.49	(1.19-1.88)	1.49	(1.19-1.88)

Model 0, 1 and 2: Separate models for PRS and depression status
All models adjusted for age, sex, calendar year, 10 principal components and genotyping batch

Model 1: Model 0 additionally adjusted for body mass index, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, prevalent diabetes, smoking status and alcohol use
Model 2: Model 1 additionally adjusted for education

Model 3: PRS and depression mutually adjusted

PRS*crime interaction $\chi^2(3)=0.73$, p=0.866
PRS (top versus bottom 12.5% share)*crime interaction $\chi^2(1)=0.21$, p=0.645
Depression*crime interaction $\chi^2(1)=2.93$, p=0.087

Supplementary table 1. Descriptive statistics of the study cohort.

	Men		Women	
	N	%	N	%
Polygenic risk score				
1 Low	2434	25.8	2566	24.3
2	2398	25.4	2602	24.6
3	2331	24.7	2669	25.3
4 High	2274	24.1	2725	25.8
Education				
Tertiary	1520	16.1	1942	18.4
Upper secondary	2058	21.8	3135	29.7
Vocational training	2808	29.8	2393	22.7
Basic	3051	32.3	3092	29.3
Smoking				
Never smoker	3894	41.3	6661	63.1
Former smoker	2720	28.8	1807	17.1
Current smoker	2823	29.9	2094	19.8
Alcohol use				
Non-drinker	1317	14.0	1963	18.6
Low moderate drinker (<35 g ethanol/week)	2448	25.9	5217	49.4
High moderate drinker (35-100 g ethanol/week)	2332	24.7	2223	21.1
Heavy drinker (>100 g ethanol per week)	3340	35.4	1159	11.0
Diabetes	767	8.1	718	6.8
	Mean	(SD)	Mean	(SD)
Age	50.0	(13.6)	48.9	(13.6)
Body mass index (kg/m2)	27.2	(4.1)	26.6	(5.2)
HDL cholesterol (mmol/l)	1.3	(0.3)	1.6	(0.4)
Total cholesterol (mmol/l)	5.5	(1.1)	5.4	(1.0)
Systolic blood pressure (mmHg)	138.8	(18.8)	133.0	(20.4)
Diastolic blood pressure (mmGh)	83.2	(11.4)	78.5	(10.8)
Total	9437		10562	

Supplementary table 2. Hazard ratios of CHD event for quartiles of polygenic risk scores and depression status by degree of urbanization.

	Model 0		Model 1		Model 2		Model 3	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Degree of urbanization								
High								
PRS								
1 Low	1.00		1.00		1.00		1.00	
2	1.39	(1.06-1.83)	1.34	(1.02-1.76)	1.33	(1.01-1.76)	1.34	(1.01-1.76)
3	1.59	(1.22-2.07)	1.55	(1.18-2.02)	1.54	(1.18-2.02)	1.54	(1.18-2.02)
4 High	2.17	(1.68-2.81)	2.04	(1.58-2.64)	2.08	(1.61-2.68)	2.06	(1.60-2.66)
Depression								
No	1.00		1.00		1.00		1.00	
Yes	1.41	(1.11-1.79)	1.41	(1.10-1.79)	1.41	(1.11-1.80)	1.39	(1.09-1.77)
Degree of urbanization								
Low								
PRS								
1 Low	1.00		1.00		1.00		1.00	
2	1.17	(0.95-1.45)	1.14	(0.92-1.41)	1.14	(0.92-1.41)	1.14	(0.92-1.41)
3	1.43	(1.17-1.75)	1.35	(1.11-1.66)	1.35	(1.10-1.65)	1.35	(1.10-1.65)
4 High	1.98	(1.63-2.40)	1.89	(1.56-2.30)	1.89	(1.55-2.29)	1.89	(1.56-2.30)
Depression								
No	1.00		1.00		1.00		1.00	
Yes	1.16	(0.94-1.43)	1.15	(0.93-1.41)	1.15	(0.93-1.41)	1.16	(0.94-1.43)

All models adjusted for age, gender, calendar year, 10 principal components and genotyping batch

Model 0, 1 and 2: Separate models for PRS and depression status; Model 1: Model 0 additionally adjusted for body mass index, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, prevalent diabetes, smoking status and alcohol use; Model 2: Model 1 additionally adjusted for education; Model 3: PRS and depression mutually adjusted

PRS*urbanization interaction $\chi^2(3)=0.52$, p=0.915
PRS (top versus bottom 12.5% share)*urbanization interaction $\chi^2(1)=1.38$, p=0.240
Depression*urbanization interaction $\chi^2(1)=0.65$, p=0.421

Supplementary table 3. Hazard ratios of CHD event for quartiles of polygenic risk scores and depression status by unemployment rate.

	Model 0		Model 1		Model 2		Model 3	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Unemployment Low								
PRS								
1 Low	1.00		1.00		1.00		1.00	
2	1.24	(0.97-1.59)	1.23	(0.96-1.57)	1.23	(0.96-1.57)	1.22	(0.95-1.57)
3	1.60	(1.27-2.03)	1.58	(1.25-2.00)	1.57	(1.24-1.99)	1.57	(1.24-1.99)
4 High	2.06	(1.64-2.59)	1.96	(1.55-2.46)	1.97	(1.56-2.48)	1.95	(1.55-2.46)
Depression								
No	1.00		1.00		1.00		1.00	
Yes	1.39	(1.13-1.72)	1.39	(1.12-1.72)	1.39	(1.12-1.72)	1.37	(1.10-1.69)
Unemployment High								
PRS								
1 Low	1.00		1.00		1.00		1.00	
2	1.24	(0.98-1.55)	1.18	(0.94-1.49)	1.17	(0.93-1.48)	1.18	(0.94-1.48)
3	1.37	(1.10-1.71)	1.30	(1.04-1.63)	1.30	(1.04-1.62)	1.30	(1.04-1.62)
4 High	2.02	(1.64-2.49)	1.95	(1.59-2.41)	1.95	(1.58-2.40)	1.95	(1.58-2.41)
Depression								
No	1.00		1.00		1.00		1.00	
Yes	1.08	(0.86-1.37)	1.06	(0.84-1.34)	1.06	(0.84-1.35)	1.06	(0.84-1.35)

Model 0, 1 and 2: Separate models for PRS and depression status; All models adjusted for age, sex, calendar year, 10 principal components and genotyping batch

Model 1: Model 0 additionally adjusted for body mass index, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, prevalent diabetes, smoking status and alcohol use; Model 2: Model 1 additionally adjusted for education; Model 3: PRS and depression mutually adjusted

PRS*unemployment interaction $\chi^2(3)=3.64$, p=0.303
PRS (top versus bottom 12.5% share)*unemployment interaction $\chi^2(1)=2.38$, p=0.123
Depression*unemployment interaction $\chi^2(1)=2.21$, p=0.137