Title: Aspirin and statin use and the subsequent development of depression in men and women: Results from a longitudinal population-based study.

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Abstract

Objective: Low-grade chronic inflammation is one potential mechanism underlying the well-established association between major depressive disorder (MDD) and increased cardiovascular morbidity. Both aspirin and statins have anti-inflammatory properties, which may contribute to their preventive effect on cardiovascular diseases. Previous studies on the potentially preventive effect of these drugs on depression have provided inconsistent results. The aim of the present paper was to assess the prospective association between regular aspirin or statin use and the incidence of MDD.

Method: This prospective cohort study included 1'631 subjects (43.6% women, mean age 51.7 years), randomly selected from the general population of an urban area. Subjects underwent a thorough physical evaluation as well as semi-structured interviews investigating DSM-IV mental disorders at baseline and follow-up (mean duration 5.2 years). Analyses were adjusted for a wide array of potential confounders.

Results: Our main finding was that regular aspirin or statin use at baseline did not reduce the incidence of MDD during follow-up, regardless of sex or age (hazard ratios, aspirin: 1.19; 95%CI, 0.68-2.08; and statins: 1.25; 95%CI, 0.73-2.14; respectively).

Limitations: Our study is not a randomized clinical trial and could not adjust for all potential confounding factors, information on aspirin or statin use was collected only for the 6 months prior to the evaluations, and the sample was restricted to subjects between 35 and 66 years of age.

Conclusion: Our data do not support a large scale preventive treatment of depression using aspirin or statins in subjects aged from 35 to 66 years from the community.

Key words: Major depressive disorder; aspirin; statins; inflammation; population-based study; longitudinal study.

Introduction

Aspirin and statins are commonly used preventive treatments against cardiovascular diseases (CVD). Aside from the anti-platelet aggregation activity of aspirin and the lipid-lowering function of statins, these medications have been postulated to have anti-inflammatory properties (Antithrombotic Trialists et al., 2009; Antonopoulos et al., 2012). Depression has been found to be associated with an increased cardiovascular risk (Baune et al., 2012; Glaus et al., 2013; Penninx et al., 2013) and low-grade chronic inflammation is a possible mechanism that could underlie this association (Baune et al., 2012). Hence, it has been suggested that the regular use of aspirin or statins could be protective against depression (Berk et al., 2013; Stafford and Berk,2011; While and Keen, 2012; Parsaik et al., 2014).

To our knowledge, the potential association between regular aspirin use and the development of major depressive disorder (MDD) has only been assessed in two Australian community studies (Almeida et al., 2010; Almeida et al., 2012; Pasco et al., 2010). One of them, a prospective study in women, found exposure to aspirin or statins (pooled) to be associated with a lower incidence of MDD over a period of 10 years (Pasco et al., 2010). The other one, a cross-sectional survey in older men, showed past but not current aspirin use to be associated with a higher prevalence of depression in the whole sample (Almeida et al., 2010), whereas subsequent analyses in a subsample revealed an interaction between aspirin use and the total homocystein (tHcy) level, indicating a reduced risk of depression only in aspirin users with a high tHcy level (Almeida et al., 2012). Regarding statins, a review of five randomized clinical trials (RCTs) and three observational studies provided mostly negative evidence for an association between these drugs and depressive symptoms (While and Keen, 2012), with negative results from all RCTs and only support for a protective effect of statins in one (Young-Xu et al., 2003) out of the three observational studies. In contrast, a recent meta-analysis of seven observational studies, which among the studies of the previous review only included the study of Young-Xu et al. (2003), documented a protective effect of statins against the development of depression (Parsaik et al., 2014). Moreover, a prospective community study of

elderly subjects not included in this meta-analysis revealed an interaction between sex and the effect of statins, with a preventive effect of these drugs on depressive symptoms over a 1.5-year period in women only (Feng et al., 2010). Finally, a recent register-based study of the Swedish population older than 40 years found differential associations for specific types of statins with depression: simvastatin was associated with a decreased risk and atorvastatin with an increased risk of depression (Redlich et al., 2014). The inconsistent results across studies are likely to be due to the large methodological variance (design, type of sample, length of follow-up, definition and assessment of depression, number and measurement of covariates) and methodological limitations including short follow-up periods particularly in the RCTs, small sample sizes, adjustment for physical covariates using self-reported rather than measured physical conditions and inaccurate assessment of depression. Indeed, with the exception of the studies of Pasco et al. (Pasco et al., 2010) and Stafford et al. (Stafford and Berk, 2011), depression was generally assessed through rating scales rather than structured interviews. These rating scales do not take into account the frequent occurrence of comorbid mental disorders and generally suffer from low positive predictive value (proportion of positively screened subjects among those who are truly affected as determined by a gold standard, i.e. in psychiatry a structured diagnostic interview) (Myers and Weissman, 1980; Roberts and Vernon, 1983; Thomas et al., 2001). Moreover, the large majority of studies determined the effect of statins on the evolution of mood symptoms rather than their potentially preventive effect on the incidence of MDD. Hence, the aim of the present paper was to assess the prospective association between regular aspirin or statin use and the incidence of MDD according to a structured diagnostic interview during a 5.2-year follow-up period in a large community sample with adjustment for a wide array of measured potentially confounding factors. Given previous findings of interactions between exposure to aspirin or statins and sex or the tHcy level regarding the incidence of MDD, we also tested the effects of sex or the tHcy level on the associations between aspirin or statin treatment and the subsequent risk of MDD.

Method

Study sample

The data of the present paper stemmed from CoLaus|PsyCoLaus (Firmann et al., 2008; Preisig et al., 2009), a cohort study designed to prospectively assess the associations between mental disorders and CVD or cardiovascular risk factors (CVRFs) in the community. The sample was randomly selected from the civil register of the city of Lausanne (Switzerland) in 2003. Sixty-seven percent of the 35 to 66 year-old participants (n=5'535) who underwent the physical exam between 2003 and 2006 also accepted the psychiatric evaluation, which resulted in a sample of 3'719 individuals (Preisig et al., 2009). In order to establish the incidence of MDD during the follow-up we had to exclude 1'624 subjects (563 men and 1061 women) with a lifetime history of MDD at baseline and the Non-Caucasians (n=168) because they had no measure of the tHcy concentration. Among the remaining 1'927 subjects, 24 died, 95 could not be traced and 134 refused participation resulting in 1'674 subjects who took part in the somatic or the psychiatric follow-up evaluations (86.8% participation). Among them, 43 subjects were excluded due to missing information on depression at follow-up. The final sample therefore consisted of 1'631 subjects (43.6% women; mean age: 51.7 years, s.d. 8.8 years). The mean follow-up duration was 5.2 years (s.d. 1.2 years), corresponding to 8'422 person-years. Compared to participants, non-participants at the follow-up had lower socio-economic status (SES; 61.2% vs. 52.7%, χ^2=7.08, p=0.01), were less physically active (58.8% vs. 49.8%, χ^2=8.13, p=0.04), suffered from overweight more frequently (50.3% vs. 59.5%, χ^2=8.21, p=0.04), reported cardiovascular events more frequently (2.3% vs. 6.5%, χ^2=15.85, p<0.001) and were more frequently exposed to aspirin (8.1% vs. 13.8%, χ^2=9.68, p=0.002). Participants and non-participants also differed by the level of alcohol intake (χ^2_2=9.60, p=0.01).

The Institutional Ethics' Committee of the University of Lausanne approved the CoLaus and subsequently the PsyCoLaus study. All participants signed a written informed consent after having received a description of the goal and funding of the study.

Measurements

Depression status and comorbid mental disorders

Diagnostic information on MDD at baseline and follow-up and comorbid anxiety and drug use disorders at baseline was collected using the French version (Leboyer et al., 1995) of the semi-structured Diagnostic Interview for Genetic Studies (DIGS), which was developed and extensively validated by the National Institute of Mental Health (Nurnberger et al., 1994). The French version of this instrument also revealed adequate inter-rater and test-retest reliability for major mood (Preisig et al., 1999) and substance use disorders (Berney et al., 2002). The DIGS was completed with sections on generalized anxiety disorder and phobias using questions from the Schedule for Affective Disorders and Schizophrenia-Lifetime and Anxiety disorder version (SADS-LA (Endicott and Spitzer, 1978)), which also revealed satisfactory test-retest reliability (Leboyer et al., 1991; Rougemont-Buecking et al., 2008). At baseline lifetime diagnoses and at follow-up the diagnosis of MDD since baseline were assigned according to the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (DSM-IV) (American Psychiatric Association, 2000). For the 162 individuals (9.9%) who were not willing to complete the DIGS interview at follow-up, MDD status at follow-up was determined using the Center for Epidemiologic Studies Depression Scale (CES-D) (Morin et al., 2011; Radloff, 1977). A score of 19 or higher was considered as an indicator of the presence of a major depressive episode (MDE) (Morin et al., 2011; Radloff, 1977). Interviewers were required to be masters-level psychologists and were trained over a two-month period. In order to provide ongoing supervision throughout the study, each interview and diagnostic assignment was reviewed by an experienced senior psychologist.

Aspirin and statin use and covariates

The assessment of regular aspirin and statin use during the 6 months prior to the baseline and follow-up physical evaluations was based on the following two questions: 1) *During the last 6 months have you taken any prescribed drugs?*; 2) *During the last 6 months have you taken any non prescribed drugs, including vitamins, herbal medicines or dietary supplements?* Participants

were then probed for the name of the drug, the reason and frequency of treatment (regular or occasional). Data were also collected on age, marital status and health-related behaviors at baseline including smoking (never, former and current), regular alcohol intake (units/week) and physical activity (no or low versus at least 20 minutes twice a week). Information on SES was derived from the DIGS and the level was assessed using the Hollingshead scale (Hollingshead, 1975). The following biological variables were either measured during the baseline physical evaluation or based on readings from venous blood samples drawn after an overnight fast: overweight (BMI ≥ 25 kg/m^2), high total cholesterol (≥ 6.2 mmol/l), high triglycerides (≥ 2.2 mmol/l), hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or drug treatment for hypertension), and diabetes (fasting blood glucose ≥ 7mmol/l or treatment for diabetes). Serum tHcy levels were determined with high performance liquid chromatography (Firmann et al., 2008). High tHcy levels were defined as concentrations ≥ 15µmol/l (Almeida et al., 2012; Nabi et al., 2013). Finally, a lifetime history of CVD was defined as a cardiovascular event (myocardial infarction, coronary insufficiency or stroke) documented in the medical records.

Statistical analysis

Analyses were performed using the Statistical Analysis System (SAS Institute Inc., Cary, NC, USA), version 9.3, for Windows. Multiple imputations were used to avoid bias related to exclusion of subjects with missing values (Sterne et al., 2009). Using the Markov Chain Monte Carlo method, we created 100 complete datasets (Schafer, 1997; White et al., 2011). Each dataset was analyzed separately and results were combined using Rubin's multiple imputation strategy (Rubin, 1987; Sterne et al., 2009). Univariate analyses were conducted using chi-square or Fisher's exact tests as appropriate. Proportional hazard models were applied (PHREG procedure (Cox, 1972)) to assess the associations between regular exposure to aspirin or statins at baseline and the incidence of MDD during the follow-up period with adjustment for socio-demographic, health-related and biological risk factors as well as comorbid

mental disorders. These models also tested interactions between the effects of sex and aspirin or statins. In subsequent analyses, associations were tested in subjects older than 50 years. The same models were applied to a restricted sample of subjects who had indicated regular use of aspirin or statins prior to both baseline and follow-up evaluations, versus non-users. In addition, associations were tested in the whole sample, including subjects who had reported MDD at baseline, using the models additionally adjusted for MDD at baseline. Finally, we aimed to test the potential effect of tHcy levels on the association between exposure to aspirin or statins and the incidence of MDD.

Results

The description of the prospective cohort of 1'631 subjects at baseline as a function of regular aspirin and statin use is presented in Table 1. Among these subjects, 45 were both regular aspirin and statin users, 87 were exposed to aspirin only and 92 to statins only during the six months prior to the baseline evaluation. Among the subjects exposed to statins, 40.2% used atorvastatin, 29.2% parvastatin, 24.8% simvastatin and 5.8% fluvastatin. The proportion of subjects who still used the drug regularly at follow-up was 50% for aspirin and 85% for statin users. Subjects exposed to aspirin and statins at baseline were older and more frequently overweight, had higher levels of triglycerides, experienced hypertension and diabetes more frequently, reported a history of CVD more frequently and reported drug use disorders less frequently than the other subjects. Users and non-users of aspirin and statins also differed by smoking status. In addition, regular statin users had lower SES and revealed a high total cholesterol level less frequently than the other subjects.

During the follow-up period 84 (9.1%) out of the 920 men and 127 (17.9%) out of the 711 women developed a first episode of MDD. As the proportional hazard model did not provide evidence for interactions between the effects of sex and aspirin ($p=0.565$) or statins ($p=0.393$) regarding the incidence of MDD, results for the whole sample are presented. The unadjusted

Hazard Ratios (HR) for regular exposure to aspirin and statins were 0.86 (95% C.I.: 0.51-1.45) and 0.93 (95% C.I.: 0.57-1.52), respectively. The results of the model with adjustment for covariates confirmed the absence of significant associations between aspirin and statin exposure and the development of MDD (Table 2). Among the covariates, diabetes and a lifetime history of anxiety disorders were predictors for the onset of MDD whereas older age (between 55 and 66 years) and moderate or high alcohol consumption were negatively associated with the incidence of MDD. Despite the absence of significant interactions between sex and aspirin and statin exposure status, the results for men and women are also provided separately in Table 2 in order to assure comparability with the findings of previous studies (Almeida et al., 2010; Almeida et al., 2012; Pasco et al., 2010).

The results hardly changed when the cohort was reduced to subjects older than 50 years (n=801). Again, there were no significant associations between the incidence of MDD and regular exposure to aspirin (HR = 0.96; 95% C.I. 0.44 - 2.03) or statins (HR = 1.08; 95% C.I. 0.55 - 2.12). Similarly, if exposure to aspirin or statins was restricted to those who indicated regular use of the drug prior to both the baseline and follow-up evaluations versus non-users (n=1'558), the HR for MDD in aspirin and statin users remained at 0.91 (95% C.I. 0.36 – 2.32) and 1.38 (95% C.I. 0.74 – 2.55), respectively. Moreover, using the incidence of a MDE during the follow-up period as the outcome variable in the whole sample of 2'830 subjects, the estimates of the effects of exposure to aspirin (HR=1.16; 95% C.I. 0.87 – 1.37) or statins (HR=0.96; 95% C.I. 0.67 – 1.37) hardly changed. In addition, we did not find any evidence for differential effects of specific types of statins on the risk of depression (results not shown here).

Regarding the potential effect of tHcy levels on the associations, only 99 subjects in our cohort revealed tHcy concentrations ≥ 15µmol/l. Interestingly, none of the 20 subjects with regular exposure to aspirin or statins developed a MDE during follow-up, whereas 7 out of the 79

subjects (8.9%) without such treatment had suffered from depression during follow-up (p=0.19 according to the Fisher's exact test).

Discussion

Our data, based on a large 35 to 66 year-old cohort which was assessed using thorough physical and psychiatric evaluations at baseline and follow-up, did not provide evidence for a preventive effect of regular aspirin or statin use on the incidence of MDD over a more than five-year follow-up period regardless of sex and age and after adjustment for a comprehensive array of potential confounders.

The absence of an association between regular aspirin or statin use and MDD contrasts with prospective studies that observed a preventive effect of these drugs on depression (Pasco et al., 2010; Young-Xu et al., 2003; Parsaik et al., 2014; Redlich et al., 2014). The discrepant results between our findings and those of the Australian community study (Pasco et al., 2010), which was based on similar methods, is most likely attributable to differences between the two cohorts. Indeed, the Australian cohort had no upper age limit whereas ours only included subjects up to 66 years. Accordingly, the Australian cohort was likely to be composed of more physically affected subjects, which was reflected by the much higher mortality rate of 26.4% vs. only 1.5% in our study. It is therefore possible that the preventive effect of aspirin and statins on depression is restricted to elderly subjects who may already have CHD. Indeed, most evidence for a preventive effect of these anti-inflammatory drugs on depression stems from three studies on mostly elderly patients treated for CHD (Otte et al., 2012; Stafford and Berk, 2011; Young-Xu et al., 2003). Unfortunately, given that only 37 subjects of our cohort had a history of CHD we could not conduct analyses in this subsample. Similarly, the subsample of subjects with high tHcy levels was also too small to draw conclusions. However, the fact that none of the subjects with high tHcy levels and regular exposure to aspirin or statins developed a MDE during follow-up was compatible with a potentially preventive effect of these drugs in more severely affected subjects. Alternatively, bias due to differential survival effects (e.g. if depression is more strongly

associated with mortality among treated subjects, who are more likely to suffer CHD, than among non-treated subjects) could also at least partially explain the association between ant-inflammatory drug use and the reduced risk of depression in more severely affected elderly cohorts. Interestingly, none of the RCTs that assessed depression symptoms (While and Keen, 2012) provided evidence for a reduction of depressive symptoms under statin treatment in mostly younger patients, which is compatible with our findings. Nevertheless, drugs that prevent the incidence of new depressive disorders do not necessarily need to reduce the level of existing depressive symptoms during treatment. The recent register-based Swedish study (Redlich et al. 2014), which however was not based on structured diagnostic interviews, suggested that inconsistent results of previous research could be attributable to differential effects of specific types of statins on depression. However, our data provide no evidence for this hypothesis.

Our findings have important implications for treatment and future research. Together with the results of RCTs our data do not support a large scale preventive treatment of depression using aspirin or statins in subjects aged 35 to 66 years from the community. However, our data cannot preclude such an effect in subjects older than 66 years of age or in patients with CHD. Interestingly, in our relatively healthy cohort previous analyses did not provide evidence for an impact of low-dose aspirin use on pro-inflammatory cytokine or high-sensitive C-reactive protein levels, either (Vaucher et al., 2014).

The results of the present study should be considered in the context of several limitations. First, our study was not a RCT and therefore it is likely that the analyses could not adjust for all confounding factors that were unequally distributed between treated and untreated subjects. Second, information on regular aspirin or statin use was collected only for the 6 months prior to the baseline and follow-up evaluations and therefore information on treatment status throughout the follow-up was missing. Moreover, we did not measure compliance to treatment. Third, the sample was restricted to subjects between 35 and 66 years of age, which impedes conclusions regarding the preventive effects of aspirin or statins in young adults and in subjects older than

66 years. Moreover, the sample was recruited in an urban area. However, although the particular features of the sample may affect the likelihood of anti-inflammatory treatment and the prevalence of depression, it is less likely that they significantly affect the prospective association between this treatment and the incidence of MDD. Fourth, for 162 subjects (10%) information on depression during the follow-up was collected using the CES-D depression scale rather than the semi-structured interview. However, the HRs (aspirin: HR = 1.17; 95% C.I. 0.66 - 2.09; statins: HR = 1.26; 95% C.I. 0.71 - 2.22) did not change after exclusion of these subjects. Fifth, although more than 200 subjects developed MDD during follow-up our sample was too small to test differential effects of regular aspirin or statin use on depression subtypes. Indeed, given the well-known large heterogeneity of MDD and findings on differential associations between its subtypes and CVRFs/CVD (Glaus et al., 2013; Penninx et al., 2013), exposure to anti-inflammatory drugs may reveal differential associations with specific MDD subtypes.

To conclude, our findings do not support a preventive effect of regular aspirin or statin use on MDD in 35 to 66 year-old adults from the community. However, the effects of these anti-inflammatory drugs in more severely affected or older subjects could not be appropriately tested in this cohort. Accordingly, in these subjects the completion of large-scale RCTs in order to further assess the potentially preventive effect of these drugs on the incidence of depression is likely to be more warranted than in relatively healthy community samples.

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Table 1: Baseline characteristics of participants as a function of aspirin and statin use (n=1'631)

	Aspirin use			Statin use		
	Yes n = 132	No n =1'499		Yes n = 137	No n = 1'494	
Characteristics	%	%	*p-value*[a]	%	%	*p-value*[a]
Sociodemographics						
Gender						
Women vs Men	46.21	43.36	*.527*	35.77	44.31	*.054*
Age (years)						
35-45	15.15	33.56		5.84	34.47	
45-54	21.21	33.96	***<.0001***	24.82	33.67	***<.0001***
55-66	63.64	32.49		69.34	31.86	
Socio-economic status						
High vs Low	51.52	46.90	*.308*	37.96	48.13	***.023***
Marital status						
Married vs Others	60.61	65.04	*.307*	67.88	64.39	*.413*
Health-related behaviors						
Smoking status						
Never	39.39	41.63		29.93	42.50	
Former	43.94	32.42	***.011***	44.53	32.33	***.006***
Current	16.67	25.95		25.55	25.17	
Alcohol intake						
No	25.00	21.75		21.90	22.02	
Low	57.58	59.11	*.664*	57.66	59.10	*.902*
Moderate or high	17.42	19.15		20.44	18.88	
Physical activity						
≥ 20 min ≥ 2/week	57.58	58.91	*.766*	53.28	59.30	*.171*
Biological risk factors						
Overweight	69.70	48.63	***<.0001***	79.56	47.66	***<.0001***
Total cholesterol ≥ 6.2 mmol/l	15.91	23.22	*.054*	15.33	23.29	***.033***
Triglycerides ≥ 2.2 mmol/l	18.94	11.81	***.017***	28.47	10.91	***<.0001***
Hypertension	57.58	29.29	***<.0001***	56.20	29.32	***<.0001***
Homocystein	8.33	5.87	*.256*	9.49	5.76	*.080*
Diabetes	15.15	4.54	***<.0001***	18.98	4.15	***<.0001***
History of CVD	21.21	0.60	***<.0001***	15.33	1.07	***<.0001***
Comorbid mental disorders						
Anxiety disorders	13.64	13.53	*.973*	15.44	13.36	*.498*
Drug use disorders	0.76	5.42	***.012***[b]	0.74	5.43	***.012***[b]

Statistically significant results are in bold.

[a] Chi-Square test.

[b] Fisher's Exact test.

Alcohol intake: low (1-6 units/week), moderate (7-13 units/week) or high (14 or more units/week).

Abbreviation: CVD= cardiovascular disease.

Table 2: Fully adjusted hazard ratios (HR) for the incidence of major depressive disorder according to aspirin and statin use (n=1'631)

	Major depressive disorder					
	All (n=1'631)		Men (n=920)		Women (n=711)	
	HR	95% CI	HR	95% CI	HR	95% CI
Aspirin and statins						
Aspirin	1.19	(0.68-2.08)	1.56	(0.63-3.88)	0.83	(0.40-1.74)
Statins	1.25	(0.73-2.14)	1.56	(0.72-3.35)	0.94	(0.41-2.14)
Sociodemographics						
Age (years)						
35-45	1 (Reference)		1 (Reference)		1 (Reference)	
45-54	0.90	(0.66-1.24)	0.81	(0.49-1.32)	0.95	(0.62-1.45)
55-66	**0.55**	**(0.37-0.81)****	**0.41**	**(0.21-0.82)***	**0.57**	**(0.33-0.95)***
Socio-economic status						
High vs Low	0.93	(0.70-1.23)	0.91	(0.58-1.42)	0.99	(0.69-1.43)
Marital status						
Married vs Others	0.75	(0.56-1.01)	0.84	(0.50-1.40)	0.82	(0.57-1.19)
Health-related behaviors						
Smoking status						
Never	1 (Reference)		1 (Reference)		1 (Reference)	
Former	1.16	(0.83-1.62)	0.96	(0.55-1.66)	1.28	(0.84-1.96)
Current	1.31	(0.92-1.87)	1.49	(0.84-2.65)	1.17	(0.74-1.86)
Alcohol intake						
No	1 (Reference)		1 (Reference)		1 (Reference)	
Low	0.94	(0.68-1.30)	1.40	(0.74-2.66)	0.84	(0.56-1.24)
Moderate or high	**0.52**	**(0.31-0.86)***	0.76	(0.34-1.68)	0.66	(0.30-1.46)
Physical activity						
≥ 20 min ≥ 2/week	1.16	(0.87-1.54)	1.49	(0.93-2.36)	0.94	(0.65-1.37)
Biological risk factors						
Overweight	0.99	(0.74-1.33)	1.30	(0.80-2.10)	1.02	(0.68-1.52)
Total cholesterol ≥ 6.2 mmol/l	1.15	(0.81-1.64)	1.28	(0.75-2.19)	1.06	(0.65-1.72)
Triglycerides ≥ 2.2 mmol/l	0.79	(0.49-1.29)	1.04	(0.57-1.90)	0.59	(0.23-1.51)
Hypertension	0.77	(0.54-1.11)	0.64	(0.36-1.13)	0.93	(0.58-1.48)
Homocystein	0.65	(0.30-1.38)	0.46	(0.14-1.48)	0.94	(0.34-2.58)
Diabetes	**1.86**	**(1.02-3.39)***	**2.27**	**(1.04-4.93)***	2.81	(0.99-8.02)
History of CVD	0.22	(0.03-1.64)	0.34	(0.04-2.87)	[a] --	--
Comorbid mental disorders						
Anxiety disorders	**1.70**	**(1.22-2.37)****	**1.98**	**(1.13-3.46)***	1.40	(0.92-2.14)
Drug use disorders	1.24	(0.72-2.13)	0.98	(0.43-2.23)	1.94	(0.92-4.11)

Statistically significant results are in bold: ** p<.01; * p<.05.

Hazard ratios from a single model adjusted for all covariates in the table.

[a] Model could not be computed due to small sample size.

Alcohol intake: low (1-6 units/week), moderate (7-13 units/week) or high (14 or more units/week).

Abbreviations: HR=hazard ratio, CI= confidence interval, CVD= cardiovascular disease.