ORIGINAL RESEARCH ARTICLE

Copeptin predicts coronary artery disease cardiovascular and total mortality

Irina Tasevska,1,2 Sofia Enhörning,1,2 Margaretha Persson,1,2 Peter M Nilsson,1,2 Olle Melander1,2

ABSTRACT

Objective In a middle-aged population, it was recently shown that the stable vasopressin marker plasma copeptin (copeptin) predicts development of diabetes mellitus, diabetic heart disease and death. Here, it was hypothesised whether copeptin predicts a risk of coronary artery disease (CAD), and cardiovascular mortality in an older population.

Methods Between 2002 and 2006, fasting plasma copeptin was examined and measured in 5386 participants of a population-based longitudinal study (mean age 69.4±6.2 years, 69.8% males) and related copeptin to risk of CAD (first myocardial infarction or coronary revascularisation), cardiovascular and total mortality during a mean follow-up time of 6.5 years using multivariate adjusted (age, gender, systolic blood pressure, antihypertensive therapy, smoking, diabetes, low-density lipoprotein and high-density lipoprotein cholesterol) Cox proportional hazards models.

Results Among subjects free from CAD at baseline, the multivariate adjusted HR (95% CI) per 1 SD increment of log-transformed copeptin for risk of CAD development was 1.20 (1.08 to 1.33) (p=0.001). There was a borderline significant interaction between diabetes and copeptin on CAD risk (p=0.08) with higher copeptin-associated risk in subjects with diabetes (1.49 (1.14 to 1.95); p=0.004) than in non-diabetic subjects (1.15 (1.02 to 1.50); p=0.02). Moreover, each SD increment of copeptin independently predicted total mortality (1.31 (1.21 to 1.41); p<0.001), an effect driven by the copeptin association with cardiovascular mortality (1.36 (1.21 to 1.53); p<0.001). The absolute risks for CAD were 4.9%, 9.3% and 2.9%, total and CV mortality were 4.9%, 9.3% and 2.9% in quartile 1, 7.1%, 9.4% and 3.5% in quartile 2, 8.3%, 14.2% and 5.6% in quartile 3, and 10.3%, 23.3% and 9.1% in quartile 4, respectively.

Conclusions Copeptin predicts development of CAD and cardiovascular mortality both in diabetics and non-diabetics.

INTRODUCTION

Coronary artery disease (CAD) is a major cause of death and is responsible for about one-third of all deaths in individuals aged >35 in developed countries.1 2 Of the classical risk factors for developing CAD (age, sex, hypertension, diabetes mellitus, hyperlipidaemia, smoking), there is particular need to understand the mechanisms underlying CAD risk related to diabetes mellitus. First, as a result of the obesity epidemic, the number of patients with diabetes worldwide is rapidly increasing, which is expected to be followed by an increased burden of diabetes-related CAD. Second, the mechanisms underlying diabetes-related CAD are largely unknown. In fact, to date there is no consistent evidence that glucose-lowering therapy reduces the risk of CAD in type 2 diabetes.3 4 There are many potential explanations for this. For example, the diabetes-related macrovascular damage may start early or even before onset of type 2 diabetes with the consequence that antidiabetic therapy is initiated too late. Alternatively, other factors than hyperglycaemia may be responsible for diabetes-related CAD. This underlines the need of identification of drug or lifestyle modifiable factors with causal relationships with both diabetes and CAD.

Arginine vasopressin (AVP) is a peptide released from the posterior pituitary gland as a response to increased plasma osmolality or decreased blood pressure. One of its functions is to promote antidiuresis by affecting the vasopressin 2 receptors in the kidneys.5 AVP is also involved in vasconstrictor action in the vessels and gluconeogenesis as well as glucogenolysis in the liver by its action on the AVP 1a receptor.6 7 8 9 Finally, by acting on the AVP 1b receptor, it mediates secretion of adrenocorticotrophic hormone, insulin and glucagon, thus suggesting a role in the glucose metabolism.10 11 A high activity of the AVP system has been related to components of the metabolic syndrome including both diabetes mellitus and hypertension.12 13 14 Studies have found that high plasma concentration of a stable fragment of the vasopressin precursor hormone, copeptin,15 predicts development of diabetes mellitus independently of known diabetes risk factors.14 16 Interestingly, in a middle-aged population (MDC) high copeptin was recently shown to independently predict CAD and death in diabetes patients but not in non-diabetic subjects.17 Thus, hyperactivity of the vasopressin system is an interesting candidate mechanism linking type 2 diabetes with diabetes-related CAD and mortality. One reason why high copeptin in middle age predicted CAD in patients with diabetes but not in non-diabetic subjects may be that any harmful vascular effects of vasopressin interact with premature vascular ageing, such as that typically seen in patients with type 2 diabetes18 on the risk of CAD development. Furthermore, hyperglycaemia has been associated with provocation of endothelial dysfunction, vascular smooth muscle cell proliferation and inflammatory phenotype changes in macrophages.19 20 A chronic glycaemic exposure has also been shown to enhance collagen cross-linking
Coronary artery disease

within the arterial wall, upregulation of enzymes degrading elastin (metalloproteinase-2 and metalloproteinase-9), as well as augmentation of the expression of angiotensin 2 receptors in vascular tissue. Based on this, the hypothesis is that in elderly subjects whose vascular age may resemble that of middle-aged patients with type 2 diabetes copeptin may predict CAD and death regardless of diabetes status. To address this issue, plasma copeptin was related to risk of CAD and death in a large population of elderly subjects and compared findings between those with and those without diabetes mellitus.

METHODS

Study population

The Malmö Preventive Project (MPP) is a Swedish single-centre prospective population-based study. Between 1974 and 1992, in all 33,346 individuals, with a homogenous ethnic background, from the city of Malmö were recruited. The recruited subjects were screened for traditional risk factors of all-cause mortality and cardiovascular disease (CVD). Between 2002 and 2006, all subjects who were alive were invited for a re-examination in which 18,240 individuals participated. Here, cardiovascular risk factors were reassessed and plasma was frozen to −80°C for later analyses. Among these 18,240 subjects, a random sample of 5,386 individuals were chosen for the current study and fasting plasma copeptin was measured in stored EDTA plasma (see below). The only exclusion criterion was prior participation in the other large population-based prospective cohort study from Malmö, that is, the Malmö Diet and Cancer study. In 18,240 participants, a number of 16,835 individuals had complete data for cardiovascular risk factors. Among these, a random sample of 5,386 subjects were selected for analysis of copeptin in relation to cardiovascular and total mortality. In analysis of incident CAD, 513 subjects who had CAD diagnosed before the baseline of the current study (i.e., before 2002–2006) were excluded, leaving 4,873 subjects for the analysis of incident CAD.

Clinical examination and assays

Participants underwent a medical history, physical examination and laboratory assessment. Blood pressure was measured using an oscillometric device twice after 10 min of rest in the supine position. Diabetes mellitus was defined as fasting plasma glucose ≥7.0 mmol/L, a self-reported physician diagnosis of diabetes or use of antidiabetic medication. Cigarette smoking was elicited by a self-administered questionnaire, with current cigarette smoking defined as any use within the past year. Measurements of fasting serum total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were made according to standard procedures at the Department of Clinical Chemistry, University Hospital Malmö. Low-density lipoprotein (LDL) cholesterol was calculated according to Friedewald’s formula. Copeptin was measured in fasted EDTA plasma using a commercially available assay in the chemiluminescence/coated tube format (B.R.A.H.M.S AG, Hennigsdorf, Germany) as described previously.

Follow-up and end point retrieval

Subjects were followed for all-cause mortality, cardiovascular mortality and a first incident CAD event until 31 December 2010, and the mean follow-up time was 6.5 years. Events were identified by linking a 10-digit personal identification number of each Swedish citizen with three registers: the Swedish Hospital Discharge Register, the Swedish Cause of Death Register and the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). The registers have been previously described and validated for classification of outcomes. CAD was defined as coronary revascularisation, fatal or non-fatal myocardial infarction, or death due to ischaemic heart disease. Myocardial infarction was defined on the basis of International Classification of Diseases, ninth revision (ICD-9) code 410 or International Classification of Diseases, tenth revision (ICD-10) code I21. Death attributable to ischaemic heart disease was defined as ICD-9 codes 412 and 414 or ICD-10 codes I22, I23 or I25. Coronary artery bypass surgery was identified from national Swedish classification systems of surgical procedures and defined as procedure codes 3063, 3066, 3068, 3080, 3092, 3105, 3127 or 3158 (the Op6 system) or procedure code FN (the KKÅ97 system). Percutaneous intervention was identified from the SCAAR. Cardiovascular mortality was defined as primary cause of death classified as ICD-9 diagnoses 390–459 and ICD-10 diagnoses 100–199.

Statistics

The distribution of copeptin was skewed to the right and therefore transformed using the natural logarithm. Copeptin was related to risk of development of CAD (first myocardial infarction or coronary revascularisation), cardiovascular and total mortality using multivariate adjusted Cox proportional hazards models. All models were adjusted for age, gender, systolic blood pressure, antihypertensive therapy, smoking, diabetes, LDL and HDL cholesterol. The proportional hazards assumption was met using weighted residuals. Two interaction terms (LN-transformed copeptin×diabetes status as well as LN-transformed copeptin×gender) were introduced on top of all other covariates to test for interaction on risk CAD and the other study outcomes.

SPSS statistical software (V22.0; SPSS, Chicago, Illinois, USA) was used for all calculations. A two-sided p value of <0.05 was considered statistically significant.

RESULTS

At the baseline of the study, the mean age was 69 years, 69.8% were males and the prevalence of diabetes was 11.7% (table 1). The mean follow-up time was 5.6±1.4 years. In the population free from prevalent CAD (n=4,873), 370 incident CAD events occurred during follow-up, and in the entire population (n=5,386), 757 individuals died of whom 284 were cardiovascular deaths. There were significant (p<0.001) correlations between copeptin and all risk factors that were subsequently adjusted for in all Cox regressions except for smoking, although the r values were generally small (r=0.079–0.197). Copeptin was positively correlated to age, systolic blood pressure, antihypertensive therapy and diabetes mellitus and negatively correlated to HDL and LDL.

In the population free from CAD at baseline, there was a 20% increased risk of CAD per 1 SD increment of log-transformed copeptin (table 2). When dividing the subjects into quartiles of copeptin, the subjects in the top quartile had a 44% increased risk of developing CAD compared with the reference quartile (table 2, figure 1). There was a borderline significant interaction between copeptin and diabetes status on the risk of CAD (p=0.08). Although the association was significant both in diabetic and non-diabetic subjects, the point estimate of the HR for CAD per 1 SD increment of log-transformed copeptin was nominally higher in diabetes subjects (1.49 (1.14 to 1.95); p=0.004) compared with that observed in the non-diabetic part of the population (1.15 (1.02 to 1.50); p=0.02). Furthermore, there was a significant interaction between copeptin and gender
for outcome of CAD (1.35 (1.07 to 1.70); p=0.013). Also, the stratified analysis in CAD for gender found that HR per 1 SD increase of copeptin in females was (1.51 (1.23 to 1.86); p<0.001) and (1.11 (0.98 to 1.26); p=0.089) in males (table 2).

A highly significant association between copeptin and increased risk of total mortality that was independent of cardiovascular risk factors (table 3) was observed. The relative risk of total mortality was >50% higher in the top versus the bottom quartile of copeptin with a significant trend over quartiles (p<0.001) (table 3 and figure 2). There was no significant interaction between copeptin and gender for outcome of total mortality (1.11 (0.94 to 1.31); p=0.230). Consequently the stratified analysis for total mortality stratified by gender showed significant results in both gender with HR per 1 SD increase of copeptin in females of (1.43 (1.22 to 1.67); p<0.001) and (1.28 (1.18 to 1.39); p<0.001) of males (table 3).

The association between copeptin and the risk of death was mainly attributable to cardiovascular mortality (table 4 and figure 3) Subjects in the top versus bottom quartile of copeptin had a 1.75-fold increase in the risk of cardiovascular mortality (table 4). In contrast to the relationship between copeptin and CAD, there was no trend towards interaction between copeptin and diabetes status on all-cause (p=0.985) and cardiovascular mortality (p=0.154). The HR for mortality (95% CI) per 1 SD increment of copeptin was 1.22 (1.03 to 1.45); p=0.023 in diabetic subjects and 1.32 (1.22 to 1.43); p<0.001 in non-diabetic subjects, whereas the corresponding HRs for cardiovascular mortality were 1.39 (1.06 to 1.81); p=0.017 in diabetic subjects and 1.32 (1.15 to 1.51); p<0.001 in non-diabetic subjects. Furthermore, there was no significant interaction between copeptin and gender for outcome of cardiovascular mortality (1.18 (0.89 to 1.56); p=0.256). Consequently, the stratified analysis for total mortality stratified by gender showed significant

| Table 2 | Copeptin versus coronary artery disease (CAD) |
|------------------------------------------------|
| **Per 1 SD HR (95% CI)** | **p Value** | **Quartile 1** | **Quartile 2** | **Quartile 3** | **Quartile 4** | **P<sub>trend</sub>** |
| CAD in all | 1.20 (1.08 to 1.33) | 0.001 | 1.0 (ref) | 1.31 (0.94 to 1.84) | 1.37 (0.98 to 1.91) | 1.44 (1.03 to 2.01) | 0.05 |
| (n=4873/370)* | (n=1261/62)* | 7.6%† | 7.1%† | 8.3%† | 10.3%† |
| CAD in males | 1.11 (0.98 to 1.26) | 0.089 | 1.0 (ref) | 1.20 (0.85 to 1.69) | 1.13 (0.80 to 1.59) | 1.12 (0.79 to 1.57) | 0.688 |
| (n=3314/294)* | (n=848/59)* | 8.9%† | 9.1%† | 9.2%† | 10.3%† |
| CAD in females | 1.51 (1.23 to 1.86) | <0.001 | 1.0 (ref) | 1.10 (0.49 to 2.47) | 1.61 (0.77 to 3.39) | 2.71 (1.35 to 5.42) | 0.001 |
| (n=1559/76)* | (n=390/11)* | 4.9%† | 3.3%† | 5.2%† | 8.3%† |

Adjusted for age, gender, LDL, HDL, systolic blood pressure, antihypertensive treatment, diabetes mellitus and smoking.

*Total number/number of cases within each category.
†Denotes absolute risk.
HDL, high-density lipoprotein; LDL, low-density lipoprotein.
results in both gender with HR per 1 SD increase of copeptin in females of 1.54 (1.17 to 2.03); p=0.002) and (1.32 (1.16 to 1.50); p<0.001) of males (table 4).

Additional adjustments for body mass index, diastolic blood pressure, pulse pressure, use of ACEi/angiotensin receptor blockers, heart failure, glucose and spironolactone were calculated and gave similar results for all end points (data not shown).

DISCUSSION

The key finding in the current study is that fasting plasma concentration of copeptin, reflecting circulating levels of vasopressin, independently predicts development of CAD, total and cardiovascular mortality in a population with a mean age of approximately 70 years. In contrast to our recent study of an MDC where copeptin predicted CAD and death exclusively in subjects with diabetes,17 the results in the current study are significant among both diabetics and non-diabetics. A trend was found towards an interaction between copeptin and diabetes on CAD risk and the point estimate of the effect size for CAD was higher among diabetic subjects compared with non-diabetic subjects. In contrast, the relationship between copeptin and total and cardiovascular mortality appeared to be equally strong in subjects with and without diabetes.

Copeptin predicts new onset diabetes14 16 and is associated with several cardiometabolic risk factors,12 13 29 and as a result, one would expect an association with hard cardiovascular end points in both diabetics and non-diabetics, but until now such an association has only been observed in subjects with diabetes. One interpretation of this is that elevated levels of circulating vasopressin may specifically contribute to diabetes-related cardiovascular risk. Our findings regarding the outcome of CAD partially support this hypothesis as there was a trend towards an interaction between copeptin and diabetes on CAD risk. On the other hand, the copeptin significantly predicted CAD, cardiovascular and total mortality both in subjects with diabetes and without. One potential explanation for these findings is that the vascular age of the current study population (mean age of approximately 70 years) is similar to the vascular age of middle-aged subjects with diabetes. Vasopressin, or any other factor that is causally related to cardiovascular disease and

Table 3  Copeptin versus total mortality

<table>
<thead>
<tr>
<th>Per 1 SD HR (95% CI)</th>
<th>p Value</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>Ptrend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality rate in all</td>
<td>&lt;0.001</td>
<td>1.0 (ref)</td>
<td>0.86</td>
<td>1.17</td>
<td>1.56</td>
<td>&lt;0.001</td>
</tr>
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<td>(1.21 to 1.41)</td>
<td></td>
<td>(n=1346/126)*</td>
<td>(n=1347/126)*</td>
<td>(n=1347/191)*</td>
<td>(n=1346/314)*</td>
<td></td>
</tr>
<tr>
<td>14%†</td>
<td></td>
<td>9.3%†</td>
<td>9.4%†</td>
<td>14.2%†</td>
<td>23.3%†</td>
<td></td>
</tr>
<tr>
<td>Total mortality rate in males</td>
<td>&lt;0.001</td>
<td>1.0 (ref)</td>
<td>1.02</td>
<td>1.26</td>
<td>1.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(1.18 to 1.39)</td>
<td></td>
<td>(n=939/104)*</td>
<td>(n=940/114)*</td>
<td>(n=940/156)*</td>
<td>(n=939/236)*</td>
<td></td>
</tr>
<tr>
<td>16.2%†</td>
<td></td>
<td>11.1%†</td>
<td>12.1%†</td>
<td>16.6%†</td>
<td>25.1%†</td>
<td></td>
</tr>
<tr>
<td>Total mortality rate in females</td>
<td>&lt;0.001</td>
<td>1.0 (ref)</td>
<td>1.67</td>
<td>1.92</td>
<td>2.30</td>
<td>0.002</td>
</tr>
<tr>
<td>(1.22 to 1.67)</td>
<td></td>
<td>(n=407/19)*</td>
<td>(n=407/35)*</td>
<td>(n=407/41)*</td>
<td>(n=407/52)*</td>
<td></td>
</tr>
<tr>
<td>9.0%†</td>
<td></td>
<td>4.7%†</td>
<td>8.6%†</td>
<td>10.1%†</td>
<td>12.8%†</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, gender, LDL, HDL, systolic blood pressure, antihypertensive treatment, diabetes mellitus and smoking.

*Total number/number of cases within each category.

†Denotes absolute risk.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
harmful and subclinical reduction of left ventricular function reduced left ventricular function increased water intake may be mentioned that in subjects with subclinical conditions such as increased water intake. Importantly, however, it should be mentioned that copeptin level is causal or not and whether it can be affected by the adverse cardiometabolic risk profile. Results encourage further studies investigating whether or not the association between copeptin and risk of cardiovascular mortality. Although copeptin was highly significant in relation to CAD only in females, there was a similar trend in males. Thus, a possible gender difference in the relationship between copeptin and CAD merits further investigation in other studies.

There are several limitations to our study. First, our study population is likely to be healthier, and thus not fully representative, compared with the average population of the corresponding age as they all survived from the initial MPP examination 1974–1992. Second, as an observational study, one does not know whether the association between copeptin and risk of cardiovascular morbidity and mortality reflects a causal relationship or not. Third, we could not adjust for measures of renal function because these measurements are lacking in our cohort. This is a clear limitation; however, in our previous study, adjustment for estimated glomerular filtration rate did not affect cardiovascular end points. Also, our hypothesis that some differences in the relation between copeptin and outcomes in diabetics and non-diabetics may be due to differences in vascular ageing is only a hypothesis as vascular ageing has various definitions. Lastly, since the diabetic population is small with only 12% of the population having diabetes at inclusion, we are underpowered to rule out non-significant interactions in CAD, CVD and total mortality. In conclusion, in contrast to our previous findings in middle-aged subjects, copeptin predicts development of CAD both in individuals with diabetes and those without in an older population free from CAD. Furthermore, copeptin strongly predicts cardiovascular mortality both in diabetics and non-diabetics. Subjects belonging to the top versus the bottom quartile of copeptin had a >70% increased risk of dying from cardiovascular disease. Since our data show a risk of development of CAD, total and cardiovascular mortality rate in both of the study populations, it does not only stress the important role of elevated levels of copeptin concerning patients with diabetes but also appears to be interesting in older, healthy individuals as well.

**Table 4** Copeptin versus cardiovascular mortality

<table>
<thead>
<tr>
<th>Per 1 SD HR (95% CI)</th>
<th>p Value</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular mortality rate in all</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.36</td>
<td>&lt;0.001</td>
<td>1.0 (ref)</td>
<td>1.00</td>
<td>1.39</td>
<td>1.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(1.21 to 1.53)</td>
<td></td>
<td>(n=5386/284)*</td>
<td>(n=1346/39)*</td>
<td>(n=1347/47)*</td>
<td>(n=1347/75)*</td>
<td>(n=1346/123)*</td>
</tr>
<tr>
<td>5.3%†</td>
<td></td>
<td>2.9%†</td>
<td>3.5%†</td>
<td>5.6%†</td>
<td>9.1%†</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular mortality in males</strong></td>
<td>&lt;0.001</td>
<td>1.0 (ref)</td>
<td>1.58</td>
<td>1.65</td>
<td>1.94</td>
<td>0.003</td>
</tr>
<tr>
<td>1.32</td>
<td></td>
<td>(n=3758/239)*</td>
<td>(n=940/53)*</td>
<td>(n=940/61)*</td>
<td>(n=939/94)*</td>
<td></td>
</tr>
<tr>
<td>6.4%†</td>
<td></td>
<td>3.3%†</td>
<td>5.6%†</td>
<td>6.5%†</td>
<td>10.0%†</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular mortality in females</strong></td>
<td></td>
<td>0.002</td>
<td>1.0 (ref)</td>
<td>2.10</td>
<td>2.63</td>
<td>0.009</td>
</tr>
<tr>
<td>1.54</td>
<td></td>
<td>(n=1628/45)*</td>
<td>(n=407/4)*</td>
<td>(n=407/9)*</td>
<td>(n=407/12)*</td>
<td>(n=407/20)*</td>
</tr>
<tr>
<td>2.8%†</td>
<td></td>
<td>1.0%†</td>
<td>2.2%†</td>
<td>2.9%†</td>
<td>4.9%†</td>
<td></td>
</tr>
</tbody>
</table>

* Total number/number of cases within each category.
† Denotes absolute risk.

Adapted for age, gender, LDL, HDL, systolic blood pressure, antihypertensive treatment, diabetes mellitus and smoking.

**Figure 3** Kaplan–Meier cardiovascular mortality rates according to quartiles of baseline copeptin levels.
Coronary artery disease

biodemarker in primary prevention. If the associations between copeptin and poor cardiovascular outcome are causal, interventions targeted at the vasopressin system appear as interesting candidates for primary prevention of CAD.

Key messages

What is already known on this subject?
It is already known that in a middle-aged population the stable vasopressin receptor plasma copeptin (copeptin) predicts development of diabetes mellitus, diabetic heart disease and mortality.

What might this study add?
This study, on the other hand, investigates whether copeptin predicts a risk of coronary artery disease (CAD) and cardiovascular mortality in an older population. Among subjects free from CAD at baseline, copeptin predicted risk of CAD development. Further copeptin also predicted risk of total mortality rate, an effect driven by the copeptin association with cardiovascular mortality.

How might this impact on clinical practice?
As the study shows that elevated levels of copeptin are independently associated with increased risk of CAD, total and cardiovascular mortality, copeptin may help physicians to sharpen cardiovascular risk stratification in order to apply optimal primary prevention.

Contributors
SE has contributed by helping to calculate and analyse the statistical parts of the article as well as contribute to write the manuscript. MP and PMN have helped with writing the manuscript as well as revising its final version. OM has contributed by drafting the Malmö Preventive Project, supervising all of the work with building the article, helping to analyse the statistical parts of the manuscript and also writing the manuscript.

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Competing interests
None declared.

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Obtained.

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Ethics committee of Lund University.

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