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Cardiovascular mortality – Comparing risk factor associations within couples and in the total population – The HUNT Study

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ABSTRACT

Background: To compare associations of conventional risk factors with cardiovascular death within couples and in the population as a whole.
Methods: We analysed baseline data (1995–97) from the HUNT2 Study in Norway linked to the national Causes of Death Registry. We compared risk within couples using stratified Cox regression.
Results: During 914776 person-years, 3964 cardiovascular deaths occurred, and 1658 of the deaths occurred among 1494 couples. There were consistently stronger associations of serum lipids and blood pressure with cardiovascular mortality within couples compared to the population as a whole. For instance, for systolic blood pressure (per 20 mm Hg), the hazard ratio (HR) within couples was 1.28 (95% confidence interval: 1.17, 1.40) compared to 1.16 (1.12, 1.20) in the total population, and for diastolic pressure (per 10 mm Hg), the corresponding HRs were 1.16 (1.07, 1.26) and 1.11 (1.08, 1.13). Anthropometric factors (BMI, waist circumference, waist-hip ratio) as well as diabetes, smoking, physical activity, and education, showed nearly identical positive associations within couples and in the total population.
Conclusions: Prospective population studies may tend to slightly underestimate associations of these factors with cardiovascular mortality.

1. Introduction

There is a large body of evidence pointing to specific factors that are likely to increase risk and mortality of cardiovascular disease. These factors include high levels of LDL and low levels of HDL cholesterol, high blood pressure, obesity, and diabetes, as well as life-style factors such as smoking, low physical activity and low socio-economic position [1–4].

Results of randomized prevention trials provide causal evidence that intervening on risk factors reduces risk of heart disease [5,6]. However, these trials are often conducted in selected populations and due to limited resources and short follow-up, outcomes are often surrogate markers, and not clinical events [7,8]. Therefore, cardiovascular risk factors have largely been determined from long-term follow-up of large population-based observational studies [9]. However, these studies are vulnerable to confounding by factors that are not randomly distributed, and statistical adjustment is typically used to handle confounding. Nonetheless, remaining residual confounding could either be due to known but unmeasured or imperfectly measured risk factors, or to factors that are not yet known to influence cardiovascular risk.

Close matching on relevant factors may also reduce confounding, and restricting the analyses to twins or siblings represents extreme examples of matching. In the context of heart disease, studies of twins or siblings provide some control for hereditary and household factors in childhood [10,11], but would not be adequate to control for factors in adulthood that are highly relevant for cardiovascular disorders. Partners tend to share life style and household factors that may not be accounted for in most studies, simply due to lack of information [12–15]. Studies of disease risk within partners may therefore be useful to adjust for shared life-style, household and other environmental factors, and maybe also for factors that originally brought the partners together. Using data from a large population study with long-term follow-up, we assessed established risk factors and cardiovascular mortality within couples,

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and compared the results with corresponding estimates obtained from the population as a whole.

2. Methods

2.1. Study population

The Nord-Trøndelag Health Study (the HUNT Study) consists of three consecutive population-based surveys conducted in a Norwegian county. In the present study, we used data from the second wave (HUNT2), to which 93,898 residents 20 years of age and older were invited between 1995 and 1997. In total, 70% (n = 65,439) attended the survey. A thorough description of the study is available elsewhere [16,17]. Briefly, it comprises extensive questionnaires, clinical examinations and blood samplings, and provides information on socioeconomic status, health related behaviour, and a broad range of self-reported symptoms and prevalent diseases. >97% of the population is Caucasian.

In the questionnaire, participants were asked to report previous cardiovascular disease, and individuals with a history of self-reported myocardial infarction or stroke were excluded from follow-up. Also, participants without information on smoking and educational status were excluded, since these variables were used in all multivariable analyses. Thus, 60,460 people were eligible for cause-specific mortality follow-up.

We performed statistical analyses in two separate samples of participants. Thus, we used the total eligible population (n = 60,460) as one sample, and the second sample consisted of all couples within the population. Statistics Norway provided information about married and cohabitating couples. After excluding 138 couples who reported not to be living together at participation in HUNT2, we could include a total of 35,554 participants among 17,777 couples. However, the analysis of couples was restricted to those where one or both partners had died from a cardiovascular cause during follow up, and therefore, 2988 participants among 1494 couples were included in the analyses of couples.

The study was approved by the Regional Committee for Medical Research Ethics in Central Norway.

2.2. Cardiovascular mortality in Norway

In the 1970s, cardiovascular mortality in Norway was among the highest in the world, but the current level is similar to that of the Mediterranean countries on the European side [18]. The temporal decline in mortality is likely to be caused by a combination of improved cardiovascular health in the population (healthier living and active cardiovascular prevention), and better and more effective treatment. A recent study indicated that changes in coronary heart risk factors accounted for about 66% of the decline in coronary heart disease events in the period from 1994 to 2010, where favorable changes in cholesterol levels may have the strongest impact [19].

2.3. Outcome ascertainment

The Norwegian Causes of Death Registry provided follow-up information on cardiovascular disease as the primary cause of death (http://www.ssb.no/english/dodsarsak), as classified according to the International Classification of Diseases (ICD)-9: 390–459; ICD-10: I00-I99. Thus, the population was followed from the date of attendance at HUNT2 (1995–97) until death from a cardiovascular cause, until death from other causes, or until the end of follow-up, 31 December 2012. Participants who emigrated from Norway during follow-up, were censored at the date of emigration.

2.4. Cardiovascular risk factors in the HUNT surveys

Prevalence of diabetes was assessed from the questionnaire, and self-reported smoking status was categorized into never, former or current smoking. Physical activity was based on WHO's recommendations [20] and categorized into low (<1 h moderate or no intensive physical activity per week), medium (<2 h moderate or <1 h intensive physical activity) or high (minimum 3 h moderate or >1 h intensive physical activity per week). Information on education was based on a record linkage with the national education database and categorized into primary education (<10 years), secondary education (11–12 years), or college/university education (>12 years).

Specially trained nurses and technicians conducted the clinical examinations [16]. The participants' blood pressure was measured three times with one-minute intervals. In the analysis we used the mean of the second and third measurement or only the second

Table 1
Characteristics of the whole population cohort and the cohort of couples within the total population. The HUNT Study, 1995–97 (HUNT2).

	Total cohort				Couple cohort			
	Death from cardiovascular disease				Death from cardiovascular disease			
	Yes		No		Yes		No	
	No.	%	No.	%	No.	%	No.	%
Mean age (SD)	73.01(10.0)		47.23(15.8)		70.44(9.6)		66.7(10.9)	
Sex								
Men	1959	49	25,979	46	1116	67	378	28
Women	2005	51	30,517	54	542	33	952	72
Diabetes								
No	3580	91	55,221	98	1514	92	1251	94
Yes	366	9	1203	2	137	8	76	6
Smoking status:								
Never smoker	1811	46	24,934	44	565	34	633	48
Former smoker	1185	30	14,791	26	627	38	381	29
Current smoker	968	24	16,771	30	466	28	316	24
Physical activity[a]:								
Low	966	34	9770	19	359	28	259	25
Medium	795	28	17,126	33	346	27	314	31
High	1085	38	25,061	48	561	44	458	44
Education level:								
Primary education	2349	59	17,015	30	865	52	667	50
Secondary education	1397	35	29,504	52	673	41	550	41
University/college	218	6	9977	18	120	7	113	9
Blood lipids, mmol/l (SD):								
HDL cholesterol	1.3(0.4)		1.4(0.4)		1.3(0.4)		1.4(0.4)	
Non-HDL cholesterol	5.2(1.3)		4.4(1.3)		5.1(1.2)		5.2(1.3)	
Triglycerides	2.0(1.2)		1.7(1.1)		2.1(1.2)		1.9(1.1)	
Blood pressure(mm Hg)(SD):								
Systolic blood pressure	158.5(24.6)		135.7(20.4)		156.1(23.9)		149.7(23.4)	
Diastolic blood pressure	87.0(13.9)		79.6(11.8)		87.0(13.2)		84.0(12.6)	
Pulse pressure	71.6(19.0)		56.1(14.1)		69.1(18.2)		65.7(16.9)	
Body mass (SD):								
Body mass index (kg/m^2)	27.4(4.3)		26.2(4.1)		27.2(4.0)		27.3(4.3)	
Waist in cm	91.9(11.6)		85.8(11.6)		93.0(10.7)		88.0(11.3)	
Waist-hip ratio	0.88(0.08)		0.84(0.08)		0.90(0.07)		0.84(0.08)	

*N varies due to missing data.
[a] Low physical activity ≤1 h moderate or no intense physical activity per week, medium physical activity ≤2 h moderate or <1 h intense physical activity and high = minimum 3 h moderate or >1 h intense physical activity per week.

measurement if the third was missing. The pulse pressure was calculated as the difference between systolic and diastolic blood pressure.

The participants' height and weight were measured wearing light clothes and without shoes. We calculated body-mass index (kg/m^2), waist and hip circumference (centimetres) and the ratio between waist and hip circumference. The waist (at the height of the umbilicus) and hip (the thickest part of the hip) measurements were performed with the participant standing and arms hanging relaxed.

The participants' blood samples were collected non-fasting, and freshly analysed at the Central Laboratory, Innherred Hospital. We used information on serum concentrations of high-density lipoprotein (HDL) cholesterol and triglycerides, and calculated non-HDL cholesterol as the difference between total cholesterol and HDL cholesterol concentrations.

The continuous cardiovascular risk factors were measured in their original scaling and for the anthropometric measures as the mean residuals divided by the standard deviation in each sex, thereby providing sex specific z scores.

2.5. Statistical analyses

We studied associations of cardiovascular risk factors with the risk of dying from cardiovascular causes during follow-up of the total population (n = 60,460) and 2988 participants among 1494 couples where one or both partners had died of a cardiovascular cause. In the analysis, cardiovascular mortality was assessed using Cox proportional hazards models with age as the time axis. The participants were followed from the age when they participated in the HUNT2 Study (1995–97) until death caused by a cardiovascular cause, deaths from other causes, emigration or until the end of follow-up (31 December 2012), whichever event occurred first.

We used Cox regression with robust standard errors in the analyses of the total population, and stratified Cox regression in the analyses of couples, where each couple was entered as a separate stratum. In the stratified Cox regression model, only couples who were discordant for exposure and timing of cardiovascular death would contribute with information to the estimates. Using this approach, we could control for factors that couples share, and confounding by factors such as socio-economic position and life style factors could therefore be minimized. We also assessed the continuous risk factors with cubic splines in order to account for possible non-linear associations [21].

In the analysis of couples, we adjusted for sex, age (as the time axis), smoking status and education, and for the total population, we also adjusted for marital status (living as a couple or not).

The proportional hazards assumptions were assessed on the basis of Schoenfeld residuals. There were indications of non-proportional hazards during follow up for some of the risk factors, and in a separate analysis, we therefore studied cardiovascular mortality before and after the time when participants reached 80 years of age in follow up. We also conducted a sensitivity analysis to assess possible reverse causality, by removing the first two years of follow-up.

We also assessed spousal associations of cardiovascular risk factors, using all 17,777 couples in the analysis. Thus, we studied the association of a certain risk factor with the partner's status for that same risk factor, using logistic regression models for dichotomous variables (diabetes, being a current smoker, being physically active and having a university or college education), and linear regression models for continuous variables (sex standardized z scores for serum concentrations of HDL cholesterol, non-HDL cholesterol, and triglycerides; systolic and diastolic blood pressure, pulse pressure, body-mass index, waist in centimetres and waist-hip-ratio). All models were performed with robust standard errors.

Precision was measured with 95% confidence intervals. Stata version 13 (www.stata.com) was used for the statistical analyses.

3. Results

Table 1 shows characteristics of the total study population and corresponding characteristics of the couples. In the total population, 3964 cardiovascular deaths occurred during 914776 person-years of follow-up. Among these deaths, 1658 occurred among 1494 couples, and among 164 of the couples, both partners died of cardiovascular causes. Median age of death of a cardiovascular cause was 83 years.

Within couples, there were strong spousal associations (web-Table 1) for smoking habits, level of education, and physical activity, and continuous risk factors, including serum lipids (HDL and non-HDL cholesterol, and triglycerides), blood pressure (systolic, diastolic, and pulse pressure), and anthropometric factors (body mass index, waist circumference, waist-hip ratio) were also positively associated within couples.

In Table 2, we show associations of established risk factors with cardiovascular mortality, both in the total population, and within couples. In the total population, all associations were in the expected direction, and the strength of the associations did not substantially differ

Table 2
Hazard ratios for cardiovascular death (ICD10: chapter I) according to different risk factors. Results from analyses in the total population and differentially exposed spouses within couples. The HUNT Study, 1995–97 (HUNT2).

	No. deaths[d]	Population[a]		No. deaths[d]	Within couples[a]	
		HR	95% CI		HR	95% CI
No diabetes	3580	1.00	Ref.	1514	1.00	Ref.
Diabetes	366	1.82	1.65–2.00	137	2.01	1.31–3.09
Smoking status:						
Never smoker	1811	1.00	Ref.	565	1.00	Ref.
Former smoker	1185	1.02	0.96–1.08	627	1.22	0.94–1.59
Current smoker	968	1.62	1.47–1.79	466	1.54	1.12–2.10
Physical activity[b]:						
Low physical activity	966	1.00	Ref.	359	1.00	Ref.
Medium physical activity	795	0.72	0.67–0.77	346	0.76	0.53–1.08
High physical activity	1085	0.64	0.60–0.68	561	0.50	0.35–0.73
Education level:						
Primary education	2349	1.00	Ref.	865	1.00	Ref.
Secondary education	1397	0.84	0.79–0.89	673	0.86	0.67–1.10
University/college	218	0.69	0.62–0.77	120	0.75	0.46–1.23
Blood lipids:						
1 mmol/L increase in HDL cholesterol	3926	0.78	0.71–0.87	1649	0.64	0.49–0.85
2 mmol/L increase in non-HDL cholesterol	3926	1.13	1.08–1.19	1649	1.16	0.99–1.37
1 mmol/L increase in triglycerides	3928	1.07	1.05–1.09	1651	1.16	1.05–1.27
Blood pressure:						
20 mm Hg increase in systolic blood pressure	3921	1.16	1.12–1.20	1646	1.28	1.17–1.40
10 mm Hg increase in diastolic blood pressure	3921	1.11	1.08–1.13	1646	1.16	1.07–1.26
Pulse pressure[c]	3921	1.08	1.06–1.10	1646	1.15	1.08–1.23
Body mass:						
1 sex specific SD increase in body mass index	3835	1.10	1.07–1.13	1636	1.10	0.98–1.24
1 sex specific SD increase in waist	3867	1.17	1.15–1.20	1637	1.19	1.06–1.34
1 sex specific SD increase in waist-hip ratio	3867	1.19	1.15–1.22	1637	1.22	1.10–1.37

[a] Adjusted for sex, age (time variable), smoking status (never, former, current), education (primary school or less, secondary education, college/university), living in a couple (population analysis only).

[b] Low physical activity ≤1 h moderate or no intense physical activity per week, medium physical activity ≤2 h moderate or <1 h intense physical activity, high physical activity = minimum 3 h moderate or >1 h intense physical activity per week.

[c] Pulse pressure = systolic-diastolic blood pressure.

[d] N varies according to missing values on exposure variables.

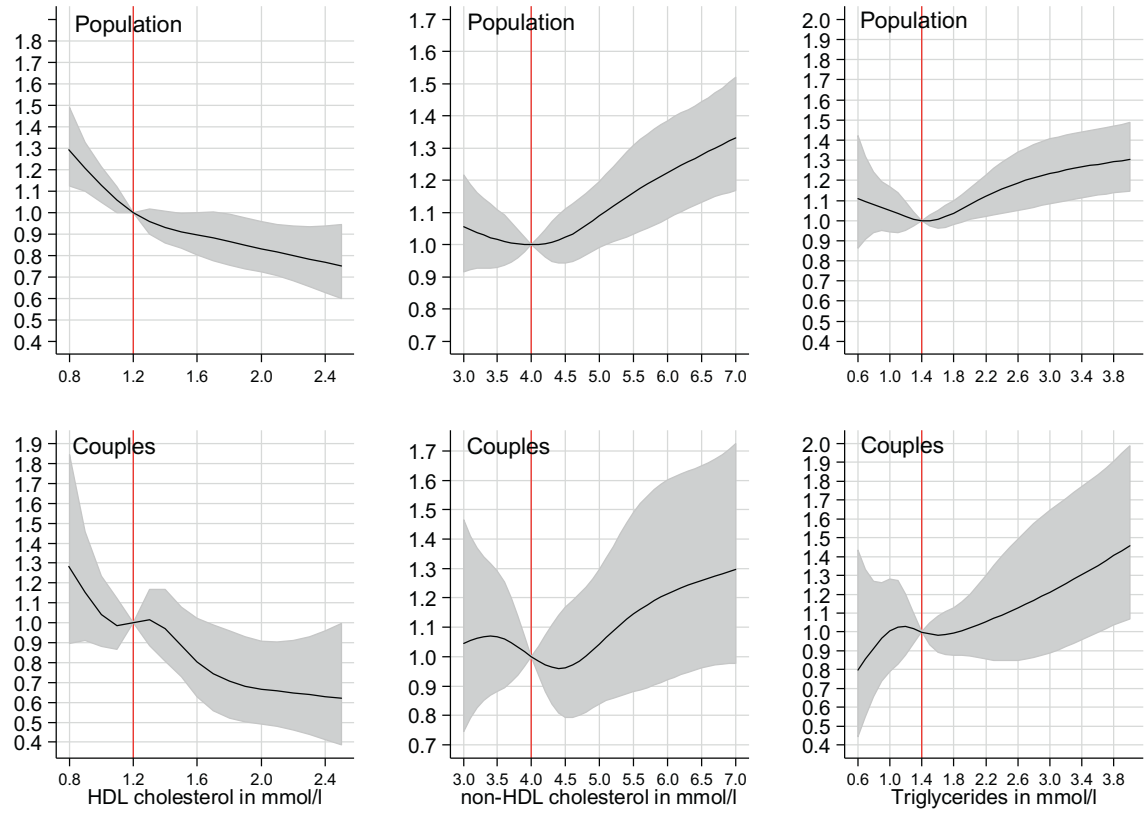

Fig. 1. Hazard ratios (y-axis) for cardiovascular mortality according to HDL cholesterol, non-HDL cholesterol and triglycerides in mmol/l (x-axis) in the total population and within couples. Shaded areas represent 95% confidence intervals. The reference value (red line) for HDL cholesterol = 1.2 mmol/L, non-HDL cholesterol = 4 mmol/L and for triglycerides = 1.4 mmol/L. All models were adjusted for sex, age (time axis), smoking status, education and living in a couple or not (population analysis only).

from that indicated by current evidence. Among couples, the categorical factors (diabetes, smoking, physical activity, education) showed similar associations as those observed for the total population. However, in the total population, the risk of cardiovascular death among former smokers did not deviate from that of never smokers (hazard ratio (HR) 1.02, 95% confidence interval (CI): 0.96, 1.08), but among couples, the point estimate of former smoking indicated an elevated risk in (HR 1.22, 95% CI: 0.94, 1.59).

Some of the continuous risk factors showed consistently stronger associations within couples than in the total population. Thus, the hazard ratio per 1 mmol/L higher HDL cholesterol was 36% lower in couples (HR 0.64, 95% CI: 0.49, 0.85), compared to 22% lower in the total population (HR 0.78, 95% CI: 0.71, 0.87). For triglycerides (per 1 mmol/L), the risk increase was 16% in couples (HR 1.16, 95% CI: 1.05, 1.27) compared to 7% in the total population (HR 1.07, 95% CI: 1.05, 1.09).

For systolic blood pressure (per 20 mm Hg), the risk of cardiovascular death was 28% higher within couples (HR 1.28, 95% CI: 1.17, 1.40) and 16% higher in the total population (HR 1.16, 95% CI: 1.12, 1.20). For pulse pressure (per 10 mm Hg), the corresponding estimates were 15% (HR 1.15, 95% CI: 1.08, 1.23) and 8% (HR 1.08, 95% CI: 1.06, 1.10) higher risk, respectively. On the other hand, the anthropometric factors (body-mass index, waist circumference, and waist-hip ratio) showed positive associations with cardiovascular mortality that were nearly identical within couples and in the total population.

The graphical analyses using cubic splines showed a linear negative association between HDL cholesterol and cardiovascular mortality both within couples and in the total population (Fig. 1). For non-HDL cholesterol, cardiovascular mortality started to increase between 4 and 5 mmol/L both within couples and in the total population. For triglycerides, there was a nearly linear positive association within couples, whereas in the total population, the association with cardiovascular mortality was J-shaped.

For blood pressure (systolic, diastolic, and pulse pressure) the associations with cardiovascular mortality displayed consistent J-shaped patterns both within couples and in the total population (Fig. 2). The figure suggests that the risk of cardiovascular death started to increase at around 120 mm Hg in systolic blood pressure, at around 75 mm Hg in diastolic blood pressure, and at around 45 mm Hg in pulse pressure (Fig. 2). These patterns were largely similar within couples and in the total population, but the risk increase within couples appeared to be consistently steeper for all three measures of blood pressure.

For anthropometric factors (Fig. 3), the risk of cardiovascular death associated with body-mass index started to increase at around 26 kg/m^2, both in men and women. For waist circumference, the risk increase started at around 85 cm in men and at 75 cm in women, and for waist-hip ratio, the corresponding risk increase started at around 0.9 for men and at 0.8 for women. The figure suggests that for each anthropometric factor, the increase in risk was consistently stronger within couples than in the total population.

3.1. Stratified analysis

In web-Tables 2 and 3, we present separate results for cardiovascular mortality until 80 years of age, and with follow-up after 80 years of age. Compared to the overall analyses, the patterns for couples and the total population were similar to those of the overall analyses, but associations were substantially stronger before 80 years of age than after the age of 80 years. Before 80 years of age, we also found that the association of former smoking in the total population did not clearly deviate from that of never smoking (HR 1.11, 95% CI: 0.98, 1.26), compared to the

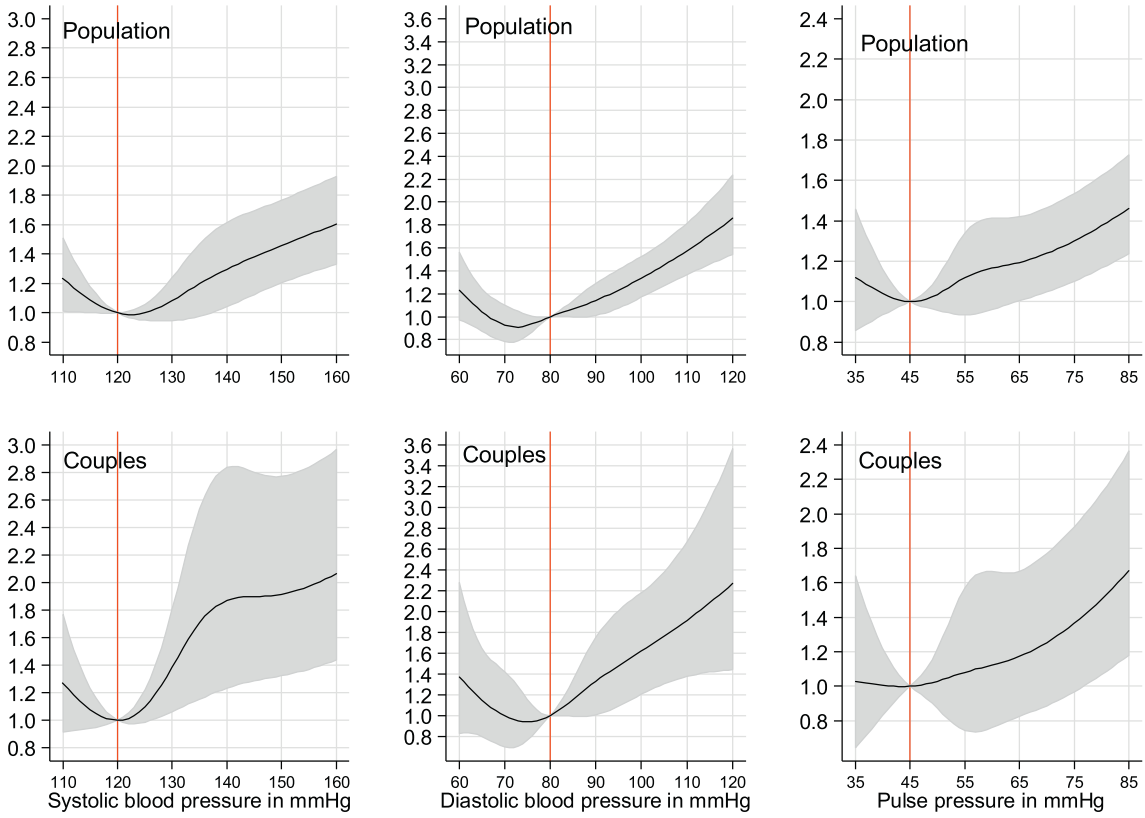

Fig. 2. Hazard ratios (y-axis) for cardiovascular mortality according to systolic, diastolic and pulse pressure in mm Hg (x-axis) in the total population and within couples. Shaded areas represent 95% confidence intervals. The reference value (red line) for systolic blood pressure = 120 mm Hg, diastolic blood pressure = 80 mm Hg and for pulse pressure = 45 mm Hg. All models were adjusted for sex, age (time axis), smoking status, education and living in a couple or not (population analysis only).

strong positive association of former smoking within couples (HR 1.61, 95% CI: 1.08, 2.40).

In a sensitivity analysis, excluding the two first years of follow-up, the results in the total population, and within couples, were nearly identical to the overall results (web-Table 4).

4. Discussion

The strength of cardiovascular risk factors has largely been determined by prospective observational studies of population-based cohorts. Since observational studies may be susceptible to confounding by unmeasured factors, we hypothesized that an analysis of couples would reduce the possibility of confounding by factors that are typically shared between partners, such as life-style, household and socioeconomic factors. In this population study with long term follow-up for cardiovascular death, we found strong support for the currently established knowledge on a range of cardiovascular risk factors. An intriguing finding of our study was the inverse association of HDL-cholesterol, and the positive associations of non-HDL cholesterol, triglycerides, and blood pressure, were consistently stronger within couples than in the total population, although precision of the estimates is a challenge.

In line with previous research [12], our findings support the hypothesis that partners share cardiovascular risk factors that are integrated in the household. Such factors may be subtle, and often difficult to capture in ordinary population studies. Nonetheless, it is reassuring that the current evidence on cardiovascular risk factors was supported by comparing differentially exposed partners within the household. The slightly stronger associations for blood pressure and serum lipids that we found within couples compared to the population as a whole, may be attributed to household factors that are likely to influence risk, such as habits of adding salt to the food, the consumption of various types of fat or sharing exercise habits. We also found that various measures of blood pressure (systolic, diastolic, and pulse pressure) displayed J-shaped associations with cardiovascular mortality both within couples and in the total population, but the risk increase displayed a steeper increase from the turning point than in the total population. On the other hand, the positive association of body mass (body-mass index, waist circumference, and waist-hip ratio) displayed a linear shape, both within couples and in the population as a whole. It is interesting to note that the risk increase was consistently steeper within couples also for anthropometric factors.

Nearly all the observed associations were slightly stronger within couples, but the difference in strength for each individual risk factor was modest and we cannot leave out chance variation as a possible explanation of these differences for each factor. However, the consistently stronger associations within couples suggest that the observed pattern is not likely to be due to chance alone.

Our findings suggest that one source of confounding could be the particular household, with its differences in life-style and socioeconomic factors that may not be captured in most studies. The close matching between partners may enable better control for rather subtle but potentially important factors for which information is usually not available. Although the couple analysis could provide improved adjustment for household factors than ordinary analysis, the analysis was restricted to couples with discordant exposure. It has been suggested that this approach might be vulnerable to selection bias and measurement error [22].

Measures of blood pressure displayed J-shaped associations, both in the total population and within couples. The J-shaped curve has often

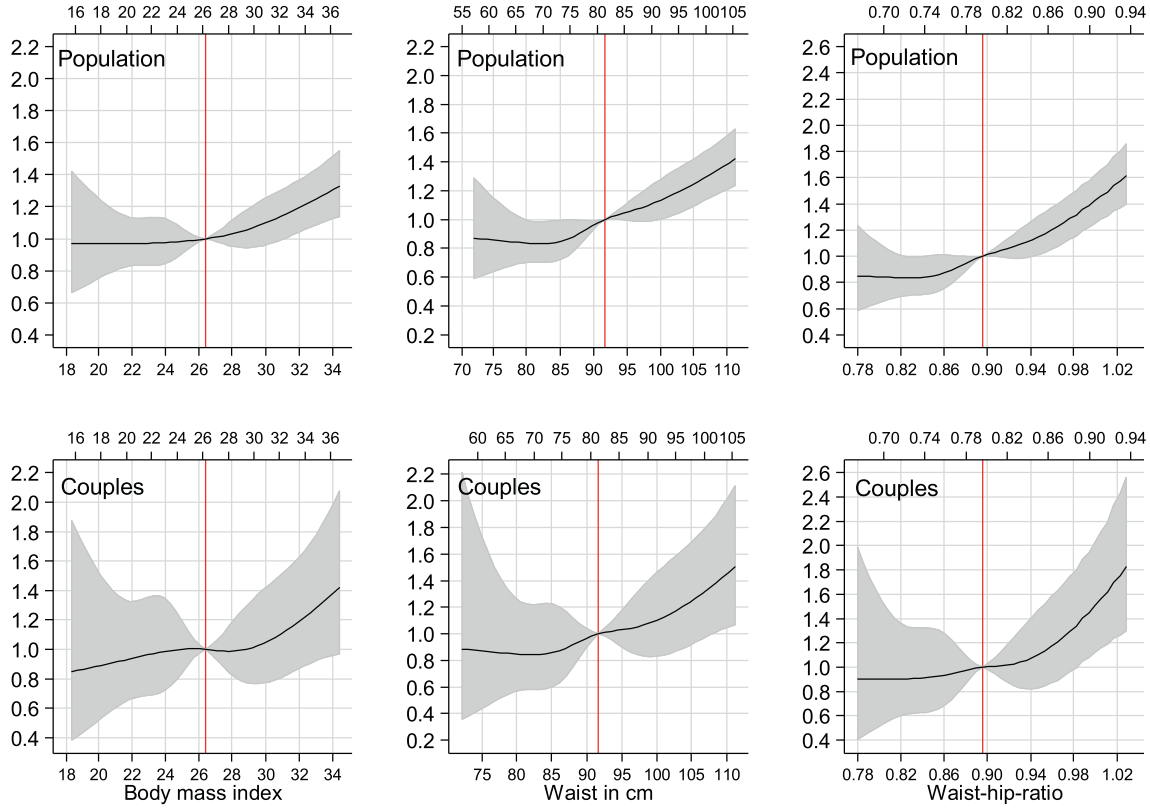

Fig. 3. Hazard ratios (y-axis) for cardiovascular mortality according to body mass index, waist in cm, and waist-hip-ratio (x-axis) in the total population and within couples. Shaded areas represent 95% confidence intervals. Measures of body mass were converted to sex-specific Z scores in the analysis. We have converted the labels back to original scale values for men (lower x-axis) and women (upper x-axis). The reference values (red line) for body mass index = 26.4 for men and 26.2 for women, waist = 91.7 for men and 81.4 for women and for waist-hip-ratio = 0.90 for men and 0.80 for women. All models were adjusted for sex, age time axis), smoking status, education and living in a couple or not (population analysis only).

been attributed to underlying or pre-clinical cardiovascular disease that could have reduced blood pressure, and subsequently resulted in premature death. For measures of body mass, we found no evidence for J-shaped associations, which may seem surprising, given previous studies that have suggested a J-shaped association of body-mass index with cardiovascular mortality [23]. A sensitivity analysis, excluding the first two years of follow-up, did not alter the J-shaped curve of the association. On the other hand, it seems plausible that a J-shaped curve related to body mass may be more relevant for other diseases than heart disease, such as for example cancer, chronic obstructive lung disease, and certain neurological diseases [24,25].

The consistently stronger associations of conventional risk factors with cardiovascular mortality that we found within couples suggest that prospective population studies may tend to slightly underestimate associations with cardiovascular mortality. Possibly, this may be due to residual confounding by household factors that are taken into account in the analysis of couples. Nonetheless, our findings are reassuring for the validity of established knowledge about cardiovascular risk factors. In clinical preventive work there is usually a strong emphasis on the patient's family history, but our results suggest that it may also be wise to pay close attention to the health of the patient's partner. By including both partners in the risk assessment and in our attempts to prevent cardiovascular disease, our findings suggest that additional gain may be achieved.

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Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.01.041.

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