

Informativeness of indices of blood pressure, obesity and serum lipids in relation to ischaemic heart disease mortality: the HUNT-II study

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Received: 23 January 2011 / Accepted: 23 March 2011 / Published online: 3 April 2011
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Abstract The informativeness of blood pressure, obesity and serum lipids associated with cardiovascular events may depend on how the indices are expressed, and mid blood pressure, waist-to-hip ratio adjusted for body-mass index (BMI) and the ratio of total to HDL cholesterol may be more informative than other expressions. Our aim was to study the informativeness of indices of blood pressure, obesity and serum lipids associated with ischaemic heart disease mortality in a large, homogeneous population. Blood pressure, weight, height, waist and hip circumference, total and HDL cholesterol, and triglycerides were measured at baseline (1995–1997) in 28,158 men and 32,573 women. Information on deaths from ischaemic heart disease (IHD) was obtained from the Causes of Death Registry in Norway from baseline until the end of 2007. Informativeness was analysed using the difference in twice the log-likelihood of a Cox model with and without each index. During 11 years of follow-up, 597 men and 418 women had died from IHD. Systolic blood pressure in men and pulse pressure in women were the most informative predictors of blood pressure, and waist-to-hip ratio adjusted for BMI was the most informative expression of obesity in both men and women. Among

serum lipids, the most informative predictor was the ratio of total cholesterol to HDL cholesterol. Using more informative expressions of conventional risk factors for ischemic heart disease may improve both the validity and precision of estimates of risk, and may be useful both clinically and for preventive purposes.

Keywords Ischaemic heart disease · Blood pressure · Obesity · Lipids · Risk · Informativeness

Introduction

Blood pressure, obesity and serum lipids are associated with the risk of ischaemic heart disease, but the preferred expression of these indices appears to change over time, maybe reflecting their evolving conceived importance [1–3]. The informativeness of an index is meant to capture how well it predicts the outcome. In relation to blood pressure, for example, mid blood pressure has been suggested to be the most informative index in relation to ischaemic heart disease mortality [4]. Similarly, among obesity indices, the ratio of waist-to-hip circumference, adjusted for body-mass index, may be the most informative predictor [5], but the ratio of waist-to-height has also been suggested [6]. Among serum lipids, the ratio of total cholesterol to HDL cholesterol may be the most informative predictor for ischaemic heart disease mortality [7].

The ranking of indicators is based on the results of meta-analyses of studies consisting of heterogeneous populations [4, 5, 7]. However, we have assessed informativeness of various indices of blood pressure, obesity and serum lipids in relation to ischaemic heart disease mortality using data from a large, homogeneous cohort, with separate analyses of men and women.

Electronic supplementary material The online version of this article (doi:10.1007/s10654-011-9572-7) contains supplementary material, which is available to authorized users.

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Methods

Study population

The adult population 20 years of age and older in Nord Trøndelag County in Norway was invited to participate in a health survey (the HUNT II Study) from August 1995 to June 1997. Briefly, 92,936 individuals were eligible to participate in the study, and 64,939 (69.9%) accepted the invitation, filled in a questionnaire that was included with the invitation letter, and attended a clinical examination conducted by trained nurses. Among other factors the examination included standardised measurements of blood pressure, body weight, body height, waist and hip circumference, and a non-fasting blood sample with subsequent measurements of total serum cholesterol, HDL cholesterol and triglycerides. The study has been described in more detail elsewhere [8].

For the present study, we excluded 769 participants with missing information on waist or hip circumference and 132 participants with missing information on total cholesterol, HDL cholesterol or triglycerides, as well as 63 participants with missing information on blood pressure and 194 participants with missing information on weight and height. We also excluded 3,050 participants with a history of myocardial infarction or stroke at baseline. Thus, 60,731 participants (28,158 men and 32,573 women) were included in the main sex-specific analyses of informativeness of predictors of ischaemic heart disease mortality.

The mortality follow-up of the HUNT cohort was approved by the regional committee for ethics in medical research, by the national Directorate of Health, and by the Norwegian Data Inspectorate.

Blood pressure, obesity and lipid indices

Systolic and diastolic blood pressure were measured using a Dinamap 845XT (Critikon) based on oscillometry, and the average of the second and third measurements was used. From these indices we calculated mean arterial pressure as the sum of systolic blood pressure and twice the diastolic blood pressure divided by three. Mid blood pressure was calculated as the average of systolic and diastolic blood pressure. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure. Pulse pressure \times Mean arterial pressure is the product of these indices.

At the clinical examination, height was measured to the nearest centimetre; weight to the nearest half kilogram; and waist and hip circumferences to the nearest centimetre. From these indices we further calculated waist-to-hip ratio, waist-to-height ratio and body-mass index (kg/m^2).

A blood sample (non-fasting) was drawn from all the participants, centrifuged at the study site, and sent in a cooler to the laboratory. Total serum cholesterol, HDL cholesterol, and triglycerides were measured on a Hitachi 911 Auto-analyzer, applying reagents from Boehringer Mannheim. The day-to-day coefficients of variation were 1.3–1.9% for total cholesterol, 2.4% for HDL cholesterol and 0.7–1.3% for triglycerides.

We calculated non-HDL cholesterol as total cholesterol minus HDL cholesterol, and the total:HDL cholesterol ratio was calculated as total cholesterol divided by HDL cholesterol.

End points

The mandatory reporting of deaths by physicians and public health officers to the national Cause of Death Registry in Norway constitutes the basis for the coding of underlying causes of death. Mortality follow-up to the Cause of Death Registry is virtually complete. In this study, the primary end point was deaths caused by ischaemic heart disease (ICD 9: 410–414; ICD 10: I 20–I 25).

Statistical analyses

Follow-up time (person-time) was calculated from the baseline date of participating in the HUNT Study until date of death, or until the end of follow-up, 31 December 2006, whichever occurred first.

We analysed informativeness of different blood pressure, obesity and lipid indices in relation to ischaemic heart disease mortality, according to the method described by Peto et al. [9]. Briefly, informativeness was calculated as the difference in twice the log-likelihood between a Cox proportional hazard model both adjusted for attained age and each respective blood pressure, obesity or serum lipid index, and a model that only adjusted for attained age. The difference between these log-likelihoods follows a chi-square distribution, and the greater the difference, the more “informative” that index is. In the analyses of waist-to-hip ratio adjusted for BMI, we included both variables simultaneously and compared with a model only adjusted for attained age.

We tested the proportional hazards assumption by comparing $-\ln(-\ln)$ survival curves and by performing tests on Schoenfeld residuals for each of the predictors of the study. If a predictor did not satisfy the proportional hazards assumption this was defined as time-dependent whenever relevant.

In addition, we analysed the area under the receiver operating curves (AUC), pseudo R^2 values from logistic regression models, estimated hazard ratios associated with one standard deviation increase, net reclassification

improvement using a 10% cut-off and integrated discrimination improvement for all predictors adjusted for attained age, and present the results as a web-only appendix for the purpose of comparison with other studies.

All statistical analyses were conducted using Stata software, release 11.1 for Windows (Stata Corp., College Station, Texas).

Results

During 11.4 years of follow-up (over 600,000 person-years) 1,015 men and women had died from ischaemic heart disease (Table 1), yielding a mortality rate of 166.8 per 100,000 person-years.

The informativeness of blood pressure indices related to ischaemic heart disease (IHD) mortality differed between men and women (Table 2). In men systolic blood pressure was the most informative index ($\chi^2_1 = 16.8$), followed by mid blood pressure ($\chi^2_1 = 16.3$), whereas in women, pulse pressure was the most informative index ($\chi^2_1 = 8.8$). Mid blood pressure, diastolic blood pressure and mean arterial pressure were the least informative indices in women.

The informativeness of expressions of obesity and serum lipids displayed similar results for men and women (Tables 3 and 4). The waist-to-hip ratio (WHR) adjusted for body-mass index was the most informative index ($\chi^2_2 = 13.6$ and $\chi^2_2 = 18.2$ for men and women, respectively) whereas WHR was slightly less informative ($\chi^2_1 = 9.7$ and $\chi^2_1 = 17.2$ for

men and women, respectively) (Table 3). However, both these indices were more informative than the waist-to-height ratio. Although the informativeness of waist circumference alone was lower than using combinations of waist and hip, or waist and height measurements, the informativeness of waist circumference alone was nonetheless higher than that of body-mass index ($\chi^2_1 = 0.1$ and $\chi^2_1 = 0.2$ for BMI in men and women, respectively) in these data.

In relation to serum lipids (Table 4), the ratio of total cholesterol to HDL cholesterol was more informative ($\chi^2_1 = 35.2$ and $\chi^2_1 = 28.3$ for men and women, respectively) than any of the other lipids in relation to IHD mortality. However, serum triglycerides showed a clear difference by sex ($\chi^2_1 = 6.8$ and $\chi^2_1 = 24.7$ for men and women, respectively), with substantially higher informativeness among women than men.

Discussion

In this prospective study of 60,731 men and women who were free from known cardiovascular disease at baseline, we assessed the informativeness of different indices of blood pressure, obesity and serum lipids in relation to IHD mortality. The most informative indices were systolic blood pressure in men and pulse pressure in women, waist-to-hip ratio adjusted for body-mass index both in men and women, and the ratio of total cholesterol to HDL cholesterol for both men and women. However, serum triglycerides also yielded high informativeness in women, but not in men.

There is evidence in the literature to support our results related to indices of obesity and serum lipids [5, 7, 10], but we were unable to find results related to blood pressure that corresponded to ours. Although it has been suggested that the waist-to-height ratio may be an informative obesity index [6], we found it to be less informative than the waist-to-hip ratio adjusted for BMI. Previously, it has been suggested that mid blood pressure may be the most informative blood pressure index [4], but in our data, this index showed relatively high informativeness in men, but not in women. We found that systolic pressure may be most informative in men, and pulse pressure in women. Previously, it has been suggested that pulse pressure may be particularly informative both in middle and old age, but with no clear difference between men and women [11].

This cohort consists of the majority of adults in a stable, homogeneous population in Norway. The population is well suited for follow-up studies, partly because of excellent national end-point registries, and partly because of the unique identification number allocated to each citizen. The prospective study design reduces the possibility of biased estimates of effect, and the large study size makes

Table 1 Characteristics of the study population (*n* = 60,731)

	Men	Women
Participants, <i>n</i> (%)	28,158 (46)	32,573 (54)
Age at baseline, years	49 (16)	50 (17)
Systolic blood pressure, mmHg	140 (19)	135 (23)
Diastolic blood pressure, mmHg	82 (12)	79 (12)
Mean arterial pressure, mmHg	101 (13)	98 (15)
Mid blood pressure, mmHg	111 (14)	107 (17)
Pulse pressure	58 (13)	57 (16)
Waist-to-hip ratio	0.90 (0.06)	0.80 (0.06)
Body-mass index, kg/m ²	26 (3)	26 (5)
Waist circumference, cm	92 (9)	81 (11)
Hip circumference, cm	102 (6)	102 (9)
Weight, kg	83 (12)	70 (12)
Total:HDL-cholesterol ratio, mmol/l	5.0 (1.7)	4.2 (1.5)
Non-HDL-cholesterol, mmol/l	4.6 (1.2)	4.4 (1.4)
Total cholesterol, mmol/l	5.8 (1.2)	5.9 (1.3)
HDL-cholesterol, mmol/l	1.2 (0.3)	1.5 (0.4)
Triglycerides, mmol/l	2.0 (1.2)	1.5 (1.0)
Deaths from ischaemic heart disease, <i>n</i>	597	418

Continuous variables are expressed as mean (SD)

Table 2 Informativeness of different blood pressure indices related to ischaemic heart disease mortality, by sex

Men	χ^2	<i>P</i>	Women	χ^2	<i>P</i>
Systolic blood pressure	16.8	<0.001	Pulse pressure	8.8	0.003
Mid blood pressure	16.3	<0.001	Pulse pressure \times mean arterial pressure	4.1	0.043
Pulse pressure \times mean arterial pressure	16.2	<0.001	Systolic blood pressure	3.0	0.086
Mean arterial pressure	15.0	<0.001	Mid blood pressure	0.7	0.393
Pulse pressure	10.3	0.001	Diastolic blood pressure	0.6	0.448
Diastolic blood pressure	9.6	0.002	Mean arterial pressure	0.2	0.687

Adjusted for attained age. Sex-specific sorted by most informative as defined by high value of χ^2

Table 3 Informativeness of different obesity indices related to ischaemic heart disease mortality, by sex

Men	χ^2	<i>P</i>	Women	χ^2	<i>P</i>
Waist-to-hip ratio adjusted for BMI	15.4	<0.001	Waist-to-hip ratio adjusted for BMI	20.3	<0.001
Waist-to-hip ratio	12.0	<0.001	Waist-to-hip ratio	19.3	<0.001
Waist-to-height ratio	11.3	<0.001	Waist-to-height ratio	8.0	0.005
Weight	2.3	0.128	Waist circumference	5.7	0.017
Waist circumference	4.0	0.044	BMI	0.2	0.671
Hip circumference	0.3	0.610	Weight	0.1	0.763
BMI	<0.1	0.808	Hip circumference	<0.1	0.873

Adjusted for attained age. Sex-specific sorted by most informative as defined by high value of χ^2

Table 4 Informativeness of different serum lipid indices related to ischaemic heart disease mortality, by sex

Men	χ^2	<i>P</i>	Women	χ^2	<i>P</i>
Total:HDL-cholesterol ratio	35.2	<0.001	Total:HDL-cholesterol ratio	28.3	<0.001
Non-HDL cholesterol	29.8	<0.001	Triglycerides	24.7	<0.001
Total cholesterol	19.1	<0.001	HDL cholesterol	17.6	<0.001
HDL cholesterol	14.5	<0.001	Non-HDL cholesterol	14.8	<0.001
Triglycerides	6.8	0.009	Total cholesterol	6.6	0.010

Adjusted for attained age. Sex-specific sorted by most informative as defined by high value of χ^2

chance an unlikely explanation of the main findings. Separate analysis of men and women is another strength of this study. In the analyses, we used the difference in twice the log-likelihood from a Cox regression model, instead of using AUC and pseudo R^2 from a logistic regression model. Our approach has the benefit of considering person-time and censoring and is likely to yield more valid estimates than the other methods [9].

Some limitations should, however, be considered. It has been suggested that the informativeness of blood pressure indices changes with age [12], and despite the large sample size, we did not have sufficient statistical power to study age-specific informativeness of these indices in detail. Furthermore, we did not have information available on non-fatal myocardial infarction or stroke and therefore, censoring for these events could not be done. Another limitation is the single measurements at one time point and no repeated measurements. Thus, we did not have data available

that allowed adjustment for possible regression dilution effects [4].

The reason for the difference in informativeness of blood pressure between men and women is uncertain, but others have suggested that pulse pressure may be particularly informative in old age [11–13] and women are usually diagnosed with ischaemic heart disease at an older age than men [14]. It has also been suggested that men and women have different patterns of arterial aging [15], and this could be of important for our findings.

The relatively low informativeness of mid blood pressure, that others have suggested to be highly informative in relation to IHD mortality [4], could be due to the lack of informativeness of diastolic blood pressure in our study, since diastolic blood pressure is a component of mid blood pressure.

The waist-to-hip ratio adjusted for BMI combines information on abdominal obesity and general obesity,

which may explain the high informativeness related to this obesity index. This combined index has also been suggested to improve informativeness in relation to all-cause mortality, especially in people with low BMI [5].

Similarly, by combining total cholesterol and HDL cholesterol to a ratio, this index was the most informative expression of serum lipids related to IHD mortality in both men and women. The superiority of combining the two measurements into a single index may simply be due to the individual strength of both total and HDL cholesterol. Serum triglycerides were especially informative in women, but not in men. The reason for the sex difference related to triglycerides is uncertain, but an imbalance between calorie intake, content and composition of diet, and a sedentary life style has been suggested [16].

Conclusions

The use of the most informative indices may improve the prediction of ischaemic heart disease mortality, and may be useful in choosing a preferred index in cardiovascular research. Also, our findings suggest that different indices of blood pressure in men and women may be useful, and that using the waist-to-hip ratio adjusted or stratified by BMI could also improve estimates of risk.

Acknowledgments Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between the Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, the Nord-Trøndelag County Council and The Norwegian Institute of Public Health. This work was supported by the Norwegian University of Science and Technology; and by the Norwegian Research Council.

Conflict of interest None.

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