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Joint effects of history of hypertension at baseline and type 2 diabetes at baseline and during follow-up on the risk of coronary heart disease

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Aims To evaluate the joint associations of history of hypertension at baseline and type 2 diabetes at baseline and during follow-up on the incidence of coronary heart disease (CHD) and CHD mortality.
Methods and results Study cohorts included 49 775 Finnish subjects aged 25–74 without history of CHD and stroke. The multivariable-adjusted hazard ratios (HRs) of CHD incidence were 1.25, 1.69, 1.25, 1.83, 1.85, 2.39, 2.15, and 3.31 (*P*-value for trend <0.001), respectively, among men with hypertension I (blood pressure 140–159/90–94 mmHg or using antihypertensive drugs at baseline but blood pressure $<160/95$ mmHg) only, with hypertension II (blood pressure $\geq 160/95$ mmHg) only, with incident diabetes during follow-up only, with both hypertension I and incident diabetes, with both hypertension II and incident diabetes, with history of diabetes at baseline only, with both hypertension I and history of diabetes, and with both hypertension II and history of diabetes compared with men without either of these diseases. The corresponding HRs of CHD incidence among women were 1.52, 2.37, 2.45, 3.78, 4.56, 5.63, 6.10, and 7.41 (*P*-value for trend <0.001), respectively. The impact on CHD mortality associated with the different strata of hypertension and diabetes was almost the same or a little stronger compared with that on the CHD incidence.
Conclusion Hypertension and type 2 diabetes increase the CHD risk independently, and their combination increases the risk dramatically, particularly in women.

Introduction

Epidemiological studies have indicated that hypertension and type 2 diabetes are commonly associated conditions and their concordance is higher than that expected. Hypertension affects up to 40% or more of diabetic patients.[1,2] High blood pressure has been found as one of the most important risk factors for coronary heart disease (CHD) in the general population[3–5] and also in patients with type 2 diabetes.[2,3,5,6] The role of type 2 diabetes as an independent risk factor for CHD has also been well established.[3,5,7–9]

Although a few studies exist about the joint prognostic effect of hypertension and type 2 diabetes on CHD risk in the general population,[3,5] it is not fully known whether the increasing risk of CHD comes from the effect of hypertension or type 2 diabetes alone, or from the combined effect of both hypertension and type 2 diabetes. Moreover, most of these studies have presented the data on history of diabetes at baseline, and only one study has the data on incident diabetes during follow-up.[10] The aim of this study is to evaluate the joint effects of hypertension of different stages at baseline and type 2 diabetes at baseline and during follow-up on the risk of CHD incidence and CHD mortality.

Methods

Subjects

Six independent cross-sectional population surveys were carried out in five geographic areas of Finland in 1972, 1977, 1982, 1987, 1992, and 1997.[11] In 1972 and 1977, a randomly selected sample making up 6.6% of the population born between 1913 and 1947 was drawn. Since 1982, the sample was stratified by area, gender, and 10-year age group according to the World Health Organization (WHO) MONICA (MONItoring trends and determinants of CArdiovascular disease) protocol.[12] The participation rate varied by year from 74–88%.[11] The subjects included in the six surveys were 25–64 years of age, and the 1997 survey also included subjects aged 65 to 74 years. Subjects who participated in more than one survey were included only in the first survey cohort. The total sample size of the six surveys was 53 166. The final sample comprised 23,851 men and 25,924 women after excluding 2138 subjects with

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the history of CHD or stroke at baseline, 105 subjects with type 1 diabetes, and 1148 subjects with incomplete data on any required variables. The participants gave an informed consent (verbal 1972–1992 and signed 1997). These surveys were conducted according to the ethical rules of the National Public Health Institute, and the investigations were performed in accordance with the Declaration of Helsinki.

Baseline measurements

A self-administered questionnaire was sent to the participants to be completed at home. The questionnaire included questions on medical history, socioeconomic factors, physical activity, smoking habits, and alcohol consumption. Education level, measured as the total number of school years, was divided into birth cohort-specific tertiles. Physical activity included occupational, commuting, and leisure-time physical activity and were merged and regrouped into three categories: low, moderate, and high.[13–16] On the basis of the responses, the participants were classified as never, ex-, and current smokers. Current smokers were categorized into those participants who smoked <20 or ≥ 20 cigarettes per day. Since questions on alcohol consumption were different between the first two surveys (1972 and 1977) and the latter surveys, the participants were categorized into abstainers and alcohol users. Family history of myocardial infarction was defined as a history of whose mothers or fathers were once diagnosed as myocardial infarction.

At the study centre, specially trained nurses measured height, weight, and blood pressure using the standardized protocol according to the WHO MONICA project.[12] Height and weight were measured without shoes and with light clothing. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in metres. Blood pressure was measured from the right arm after 5 min of sitting. After blood pressure measurement, a venous blood specimen was taken. Total cholesterol was determined by using Lieberman Burchard method in 1972 and 1977 and by an enzymatic method (CHOD-PAP, Boehringer MANNHEIM, Mannheim, Germany) since 1982. Because the enzymatic method gave 2.4% lower values than the Lieberman Burchard method, the values measured in 1972 and 1977 were corrected by this percentage. All samples were analysed in the same central laboratory at National Public Health Institute.

Assessment of hypertension at baseline and diabetes at baseline and during follow-up

Assessment of diabetes status was based on self-reporting and on the data of two nationwide registers. The National Hospital Discharge Register data included information on hospital discharge diagnosis from 1968 through the end of 2002. Data on diabetes medication were obtained from the National Social Insurance Institution's register on special reimbursement for glucose-lowering drugs from 1964 through the end of 2002. Glucose-lowering drugs prescribed by a physician are free of charge in Finland and are subject to approval of a physician who reviews each case history. The physician confirms the diagnosis of diabetes by applying the WHO criteria. All patients receiving free medication (either oral glucose-lowering agents or insulin) are entered into a register maintained by the National Social Insurance Institution. Subjects who reported having diabetes on the questionnaire, or who had had a hospital discharge diagnosis of diabetes, or the approval for free-of-charge medication for diabetes before the baseline survey were classified as having history of diabetes at baseline. Subjects who had the first hospital discharge diagnosis with diabetes, or the approval for free-of-charge medication for diabetes after the baseline survey were classified as having incident diabetes during follow-up.

Data on the initiation of antihypertensive drug treatment were also received from the records of the Social Insurance Institution's nationwide register on persons entitled to special reimbursement for antihypertensive drugs since 1964. Hypertension stage I was defined as systolic blood pressure 140–159 mmHg and/or diastolic blood pressure 90–94 mmHg, or using antihypertensive medicine according to the questionnaire or the approval of special reimbursement for antihypertensive drugs before the baseline survey but blood pressure at the survey examination <160 mmHg systolic and <95 mmHg diastolic. Hypertension stage II was defined as systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg. The normotensive reference group was defined as systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg and without any antihypertensive drugs treatment at baseline.

Prospective follow-up

Follow-up information was based on the Finnish Hospital Discharge Register for non-fatal outcomes (hospitalized myocardial infarctions) and the Finnish Death Register for fatal outcomes (deaths due to CHD) by using social security numbers assigned to every citizen of Finland. The overall sensitivity of the diagnosis of myocardial infarction in the combined Finnish Hospital Discharge Register and the Causes of Death Register was 83%.[17] Combined non-fatal myocardial infarction and fatal CHD cases were defined as the incident CHD events in the analysis. Follow-up data were available through 31 December 2004. The Eighth, Ninth and 10th Revisions of the International Classification of Diseases (ICD) were used to identify non-fatal myocardial infarction (410–411 and I21–I22, I24) and fatal cases of CHD (410–414 and I20–I25) cases.

Statistical analyses

The Cox proportional hazards model were used to estimate the hazard ratios (HRs) of CHD incidence and CHD mortality among participants in nine groups: subjects with neither hypertension nor diabetes, with hypertension I only, hypertension II only, incident diabetes during follow-up only, both hypertension I and incident diabetes, both hypertension II and incident diabetes, history of diabetes at baseline only, both hypertension I and history of diabetes, and subjects with both hypertension II and history of diabetes. The proportional hazards assumption in the Cox model was assessed with graphical methods and with models including time-by-covariate interactions.[18] In general, all proportionality assumptions were appropriate. In addition, the association of blood pressure (as a continuous variable) with the risk of CHD was analysed stratifying by the diabetes status. The analyses were first carried out adjusting for age, and study year, and further also for BMI, total cholesterol, education, smoking, alcohol consumption, physical activity, and family history of myocardial infarction. A χ^2 log-likelihood ratio test was carried out to test the significance of the interaction terms of hypertension and diabetes on coronary risk. Likelihood ratio test for interaction was also carried out to determine whether the effect of hypertension and diabetes on coronary risk was different in men and women. A $P < 0.05$ (two-sided) was considered as statistically significant. All statistical analyses were performed with SPSS for Windows 15.0 (SPSS Inc., III, Chicago, USA).

Results

General characteristics of the study population at baseline are presented in *Table 1*. During a median follow-up of 21.5 years (12.8 and 27.8 years for the 25th and the 75th quartiles, respectively), 5074 incident CHD events were recorded, of which 3134 were fatal.

When blood pressure was used as a continuous variable, multivariable-adjusted (age, study year, BMI, total cholesterol, education, smoking, alcohol drinking, physical activity, and family history of myocardial infarction) HRs of

Table 1 Baseline characteristics of study subjects by sex

	Men ($n = 23\,851$)	Women ($n = 25\,924$)
Age (years)	43.9 (11.3)[a]	44.4 (11.3)
BMI (kg/m^2)	26.2 (3.7)	26.0 (4.8)
Systolic blood pressure (mmHg)	143 (19)	139 (23)
Diastolic blood pressure (mmHg)	88 (12)	84 (12)
Total serum cholesterol (mmol/L)	6.16 (1.25)	6.07 (1.33)
Education (years)	9.3 (3.9)	9.5 (3.9)
Blood pressure status (%)[b]		
No hypertension	36.4	50.1
Hypertension I	32.4	25.6
Hypertension II	31.2	24.3
Diabetes status (%)		
No diabetes	92.1	92.5
Incident diabetes during follow-up	6.0	5.8
History of diabetes at baseline	1.9	1.7
Family history of myocardial infarction (%)	23.6	25.6
Current smoking (%)	42.5	17.2
Low physical activity (%)	7.2	9.9
Alcohol drinker (%)	65.4	35.2

[a]Mean (standard deviation).

[b]No hypertension was defined as blood pressure <140/90 mmHg and without any antihypertensive drugs treatment at baseline. Hypertension stage I was defined as blood pressure 140–159 and/or 90–94 mmHg, or with any antihypertensive drugs treatment at baseline but blood pressure <160/95 mmHg. Hypertension stage II was defined as blood pressure ≥160/95 mmHg at baseline.

CHD incidence among men were 1.22 (95% CI 1.18–1.26) for a 20 mmHg increment in systolic blood pressure and 1.18 (95% CI 1.15–1.22) for a 10 mmHg increment in diastolic blood pressure (*Table 2*). The corresponding multivariable-adjusted HRs among women were 1.26 (95% CI 1.21–1.30) and 1.23 (95% CI 1.18–1.28). The association of blood pressure with the risk of CHD was a little stronger among non-diabetic subjects than subjects with diabetes both during follow-up and at baseline. CHD incidence was increased by 23% (95% CI 1.10–1.37) in men with incident diabetes during follow-up and by 90% (95% CI 1.59–2.27) in men with history of diabetes at baseline compared with non-diabetic men. In women, CHD incidence was increased by 2.04 times (95% CI 1.80–2.30) and 3.7 times (95% CI 3.02–4.53), respectively.

Compared with men and women without hypertension or diabetes, age- and study year-adjusted HRs of CHD incidence associated with hypertension I only, with hypertension II only, with incident diabetes during follow-up only, with both hypertension I and incident diabetes, with both hypertension II and incident diabetes, with history of diabetes at baseline only, with both hypertension I and history of diabetes, and with both hypertension II and history of diabetes were 1.35, 1.98, 1.45, 2.25, 2.43, 2.54, 2.28, and 3.65 (*P*-value for trend <0.001) in men, and 1.61, 2.61, 2.86, 4.20, 5.32, 5.88, 6.65, and 8.66 (*P*-value for trend <0.001) in women, respectively (*Table 3*). The corresponding HRs of coronary mortality were 1.54, 2.44, 1.28, 1.82, 2.60, 3.27, 3.23, and 4.81 (*P*-value for trend <0.001) in men and 1.70, 3.02, 3.49, 3.78, 6.40, 7.92, 10.3, and 13.3 (*P*-value for trend <0.001) in women, respectively (*Table 4*). Further adjustments for other risk factors did not appreciably change these risk estimates. The interaction terms of hypertension and diabetes on both CHD incidence ($\chi^2 = 7.43$ in men and 6.79 in women, 4 d.f., both $P > 0.1$) and CHD mortality ($\chi^2 = 2.32$ in men and 5.38 in women, 4 d.f., both $P > 0.1$) were not statistically significant, indicating that these two factors operated independently for the CHD risk.

Compared with men and women without hypertension and diabetes, the relative risks of incident CHD and CHD mortality were higher in women than in men with any combination of hypertension and diabetes. This sex difference was, however, statistically significant for only CHD incidence among subjects with hypertension I only ($\chi^2 = 4.31$, 1 d.f., $P < 0.05$), and for both CHD incidence and CHD mortality among subjects with hypertension II only ($\chi^2 = 20.46$ and 9.0, 1 d.f., $P < 0.001$ and $P < 0.005$), with incident diabetes during follow-up only ($\chi^2 = 8.47$ and 10.36, 1 d.f., both $P < 0.005$), with both hypertension I and incident diabetes ($\chi^2 = 23.16$ and 17.44, 1 d.f., both $P < 0.001$), with both hypertension II and incident diabetes ($\chi^2 = 50.46$ and 34.64, 1 d.f., both $P < 0.001$), with history of diabetes at baseline only ($\chi^2 = 6.02$ and 4.15, 1 d.f., $P < 0.025$ and $P < 0.05$), with both hypertension I and history of diabetes ($\chi^2 = 17.91$ and 14.51, 1 d.f., both $P < 0.001$), and with both hypertension II and history of diabetes ($\chi^2 = 16.85$ and 17.07, 1 d.f., both $P < 0.001$).

Discussion

This study indicated that both hypertension and type 2 diabetes were independently associated with an increased risk of the incidence of CHD and CHD mortality. Blood pressure was associated with the risk of CHD in a similar fashion both in diabetic and non-diabetic subjects, but the absolute rates were higher in diabetic patients. The highest risk of an incident CHD event, and in particular of CHD death, was found among subjects who had both history of hypertension and history of diabetes; it is probably due to a longer duration of these conditions compared with people whose diabetes was diagnosed during the follow-up.

High blood pressure is one of the most important risk factors for CHD in all ethnic groups.[4] The association between blood pressure and CHD mortality is strong and direct, and the absolute risk of CHD mortality associated with high blood pressure increases with age.[4] However, most studies of hypertension and CHD risk have not stratified for the diabetes status or have used only history of diabetes as a confounder in analyses. We found that this direct association between blood pressure and the CHD risk was consistent among both diabetic and non-diabetic subjects. Several studies have demonstrated that hypertension, or an increase in systolic blood pressure, is independently associated with an increased risk of CHD in the diabetic patients.[2,3,5,6] It is also known that hypertension predicts the development of type 2 diabetes.[19] Prevalent type 2 diabetes is a well-established risk factor for CHD[3,5,7–9] Epidemiological studies have indicated that patients with type 2 diabetes have a two to four times higher risk of CHD mortality than those without diabetes,[3,5,7–9,20] and diabetic women show a higher relative risk for cardiovascular disease than diabetic men.[9,20,21] An important question is, however, to

Table 2 Hazard ratios for coronary heart disease incidence and mortality according to continuous blood pressure levels or the status of diabetes[a]

	HRs (95% CIs)			
	CHD incidence		CHD mortality	
	Men	Women	Men	Women
All subjects ($n = 23851$ in men; $n = 25924$ in women)				
SBP, per 20 mmHg increment	1.22 (1.18–1.26)	1.26 (1.21–1.30)	1.33 (1.27–1.38)	1.31 (1.25–1.37)
DBP, per 10 mmHg increment	1.18 (1.15–1.22)	1.23 (1.18–1.28)	1.24 (1.20–1.29)	1.26 (1.20–1.32)
Diabetes				
No	1.00	1.00	1.00	1.00
Incident diabetes during follow-up	1.23 (1.10–1.37)	2.04 (1.80–2.30)	0.99 (0.85–1.15)	1.99 (1.71–2.31)
History of diabetes at baseline	1.90 (1.59–2.27)	3.70 (3.02–4.53)	2.11 (1.70–2.60)	4.87 (3.85–6.15)
Subjects without diabetes ($n = 21970$ in men; $n = 23970$ in women)				
SBP, per 20 mmHg increment	1.23 (1.18–1.27)	1.29 (1.23–1.35)	1.33 (1.27–1.40)	1.35 (1.27–1.42)
DBP, per 10 mmHg increment	1.20 (1.16–1.24)	1.28 (1.22–1.34)	1.27 (1.22–1.32)	1.33 (1.25–1.41)
Subjects with incident diabetes during follow-up ($n = 1420$ in men; $n = 1503$ in women)				
SBP, per 20 mmHg increment	1.22 (1.10–1.35)	1.18 (1.09–1.28)	1.41 (1.23–1.61)	1.23 (1.12–1.35)
DBP, per 10 mmHg increment	1.10 (1.01–1.20)	1.15 (1.06–1.25)	1.16 (1.04–1.30)	1.20 (1.09–1.32)
Subjects with history of diabetes at baseline ($n = 461$ in men; $n = 451$ in women)				
SBP, per 20 mmHg increment	1.08 (0.93–1.27)	1.21 (1.02–1.43)	1.16 (0.97–1.39)	1.29 (1.06–1.56)
DBP, per 10 mmHg increment	1.03 (0.90–1.18)	1.03 (0.87–1.22)	1.05 (0.90–1.23)	1.00 (0.83–1.21)
Subjects with diabetes both at baseline and during follow-up ($n = 1881$ in men; $n = 1954$ in women)				
SBP, per 20 mmHg increment	1.19 (1.09–1.29)	1.18 (1.09–1.26)	1.32 (1.18–1.47)	1.22 (1.12–1.32)
DBP, per 10 mmHg increment	1.07 (1.00–1.15)	1.11 (1.03–1.19)	1.11 (1.01–1.21)	1.12 (1.03–1.22)

SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a]Multivariable models included age, study year, BMI, total cholesterol, education, smoking, alcohol drinking, physical activity, family history of myocardial infarction, diabetes, and systolic blood pressure (or diastolic blood pressure).

what extent asymptomatic diabetes, new-onset diabetes during follow-up, and impaired glucose tolerance are related to the risk of CHD.[8,10,20] It has been shown that about half of the type 2 diabetes patients and most of the people with impaired glucose tolerance are unaware of their condition, if not tested for glucose tolerance.[22] Also, it is known that diabetes may remain undiagnosed for over 10 years,[23] and during this period, hyperglycaemia (including asymptomatic diabetes, new-onset diabetes during follow-up, and impaired glucose tolerance) may cause cardiovascular disease.[8,10,20] Furthermore, although hypertension is very common in patients with type 2 diabetes,[1] only a few studies assessed the joint effect of hypertension and type 2 diabetes on the CHD risk in the general population. Our results suggest that, in order to reduce CHD risk, it is necessary to consider carefully the treatment strategies based on the individual disease status, including both hypertension and diabetes and their combination. Because we did not have data on the active management of hypertension and diabetes during the follow-up, our predictions may underestimate the risk since potential treatment benefits were not taken into account.

Recently, clinical trials have shown that pharmacological treatments of hypertension are efficient ways to prevent CHD in hypertensive patients.[24,25] A meta-analysis based on 18 randomized trials found that low-dose diuretic therapy was effective in preventing CHD mortality.[24] For diabetic patients, blood pressure lowering therapy seems to offer a greater reduction in the risk of macrovascular disease than do interventions for blood glucose control.[26,27] This is probably in part due to the fact that currently we have more efficient tools to lower blood pressure than to control hyperglycaemia. In antihypertensive therapy, the recent guidelines have recommended to control both systolic and diastolic blood pressures, although prior to the results from trials on isolated systolic hypertension[28,29] the emphasis was on diastolic pressure. In anti-diabetic therapy, the emphasis is still largely on the control of fasting hyperglycaemia, not post-prandial (post-challenge) hyperglycaemia. Observational studies have, however, provided undisputed evidence that cardiovascular risk largely depends on post-prandial (post-challenge) glucose, not on fasting glucose.[8] This may be another reason for poor impact of anti-diabetic treatment on cardiovascular risk. Several clinical trials have demonstrated that adequate control of hypertension attenuates the risk of CHD in hypertensive diabetic patients,[24,25,30,31] even to the level of non-diabetic patients.[25]

There are several strengths and limitations in our study. We have a unique possibility to stratify not only for the baseline but also for follow-up status of diabetes. The number of participants was large and from a homogeneous population. The median follow-up, 21.5 years, was long and resulted in a very large number of CHD events. Because of computerized register linkage, the event ascertainment was complete. A limitation of our study was that we did not carry out

Table 3 Hazard ratios for coronary heart disease incidence according to status of hypertension and diabetes

	HRs (95% CIs)					
	Men			Women		
	No hypertension	Hypertension I	Hypertension II	No hypertension	Hypertension I	Hypertension II
No diabetes						
Numbers of participants	8297	7142	6531	12 587	6055	5328
Numbers of cases	612	878	1327	212	370	697
Person-years	151 508	137 660	117 205	245 868	126 333	111 157
Adjustment for age and study year	1.00	1.35 (1.21–1.49)	1.98 (1.80–2.19)	1.00	1.61 (1.35–1.91)	2.61 (2.22–3.06)
Multivariable adjustment[a]	1.00	1.25 (1.13–1.39)	1.69 (1.53–1.87)	1.00	1.52 (1.28–1.81)	2.37 (2.01–2.79)
Incident diabetes during follow-up						
Numbers of participants	274	444	702	291	434	778
Numbers of cases	46	117	207	31	96	249
Person-years	6297	9496	14 434	7299	9862	17 284
Adjustment for age and study year	1.45 (1.07–1.96)	2.25 (1.85–2.75)	2.43 (2.07–2.84)	2.86 (1.96–4.17)	4.20 (3.28–5.36)	5.32 (4.40–6.42)
Multivariable adjustment[a]	1.25 (0.93–1.69)	1.83 (1.50–2.25)	1.85 (1.56–2.18)	2.45 (1.67–3.57)	3.78 (2.94–4.85)	4.56 (3.73–5.58)
History of diabetes at baseline						
Numbers of participants	121	144	196	117	135	199
Numbers of cases	26	34	67	13	30	62
Person-years	1732	2088	2413	1863	1887	2932
Adjustment for age and study year	2.54 (1.71–3.76)	2.28 (1.61–3.22)	3.65 (2.83–4.71)	5.88 (3.35–10.3)	6.65 (4.51–9.80)	8.66 (6.49–11.6)
Multivariable adjustment[a]	2.39 (1.61–3.55)	2.15 (1.52–3.04)	3.31 (2.56–4.28)	5.63 (3.20–9.88)	6.10 (4.13–9.02)	7.41 (5.53–9.94)

[a]Multivariable models were adjusted for age, study year, BMI, total cholesterol, education, smoking, alcohol drinking, physical activity, and family history of myocardial infarction.

Table 4 Hazard ratios for coronary heart disease mortality according to status of hypertension and diabetes

	HRs (95% CIs)					
	Men			Women		
	No hypertension	Hypertension I	Hypertension II	No hypertension	Hypertension I	Hypertension II
No diabetes						
Numbers of participants	8297	7142	6531	12 587	6055	5328
Numbers of cases	303	530	901	95	210	459
Person-years	154 598	141 929	123 140	246 859	128 163	113 835
Adjustment for age and study year	1.00	1.54 (1.34–1.77)	2.44 (2.14–2.78)	1.00	1.70 (1.33–2.17)	3.02 (2.41–3.79)
Multivariable adjustment[a]	1.00	1.45 (1.26–1.67)	2.06 (1.81–2.36)	1.00	1.60 (1.25–2.05)	2.70 (2.14–3.41)
Incident diabetes during follow-up						
Numbers of participants	274	444	702	291	434	778
Numbers of cases	22	55	128	20	53	183
Person-years	6527	10 283	15 548	7431	10 351	18 292
Adjustment for age and study year	1.28 (0.83–1.97)	1.82 (1.37–2.43)	2.60 (2.11–3.19)	3.49 (2.16–5.66)	3.78 (2.69–5.32)	6.40 (4.97–8.25)
Multivariable adjustment[a]	1.08 (0.70–1.67)	1.43 (1.07–1.91)	1.95 (1.57–2.42)	2.90 (1.78–4.71)	3.34 (2.36–4.71)	5.28 (4.05–6.90)
History of diabetes at baseline						
Numbers of participants	121	144	196	117	135	199
Numbers of cases	18	26	49	8	23	51
Person-years	1818	2155	2609	1906	1954	3100
Adjustment for age and study year	3.27 (2.03–5.26)	3.23 (2.16–4.83)	4.81 (3.55–6.52)	7.92 (3.84–16.3)	10.3 (6.49–16.4)	13.3 (9.39–18.8)
Multivariable adjustment[a]	3.09 (1.92–4.97)	3.08 (2.06–4.61)	4.21 (3.09–5.73)	7.85 (3.80–16.2)	9.24 (5.80–14.7)	10.8 (7.61–15.4)

[a]Multivariable models were adjusted for age, study year, BMI, total cholesterol, education, smoking, alcohol drinking, physical activity, and family history of myocardial infarction.

either fasting glucose test or glucose tolerance test at the baseline. Therefore, we have missed cases of asymptomatic diabetes at baseline, but many of them were ascertained as incident cases of diabetes during the follow-up. Another limitation was that we did not have data on individual drugs used for the treatments of hypertension and diabetes, but with such a long duration of the observational study it would be almost impossible to reveal effects due to specific pharmacological agents, since their use has varied drastically over time in most if not all of hypertensive and diabetic patients. Finally, we cannot completely exclude the effects of residual confounding due to measurement errors in the assessment of confounding factors or some unmeasured dietary, social, and other factors.

In conclusion, our study confirmed that both hypertension and type 2 diabetes increased the risk of CHD independently, but in people who had both of them together, the risk increased dramatically. Since hypertension and type 2 diabetes often occur concomitantly, it is possible that part of the risk of CHD assumed to be related to high blood pressure may primarily be due to undiagnosed disorders in glucose metabolism since blood pressure values are recorded much more often than glucose values, in particular post-challenge glucose. This has to be assessed in studies where adequate data also on glucose tolerance have been collected.

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Clinical vignette

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The LEOPARD syndrome: a rare condition associated with hypertrophic cardiomyopathy

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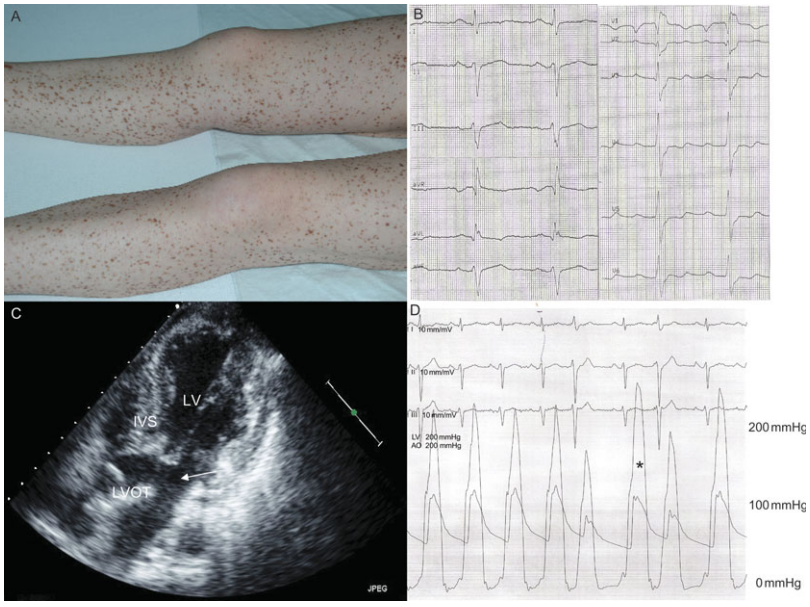

A 66-year-old woman, known for years with LEOPARD syndrome (LEOPARD stands for multiple Lentigines, Electrocardiographic conduction defects; Ocular hypertelorism; Pulmonary stenosis; Abnormalities of the genitalia; Retardation of growth and sensorineural Deafness), presented with complaints of progressive dyspnoea over the course of the last months. The physical examination revealed multiple lentigines, café-au-lait spots (Panel A), and pectus excavatum. The 12-lead ECG (Panel B) showed left-axis deviation, ST-segment abnormalities, and T-wave inversion. An echocardiographic analysis confirmed the diagnosis of hypertrophic obstructive cardiomyopathy (HOCM) with a maximal septal wall thickness of 19 mm, a left ventricular outflow tract (LVOT) dynamic gradient of 73 mmHg, and systolic anterior movement of the mitral valve (Panel C). A right and left ventricular catheterization was performed, confirming the diagnosis of HOCM (Brockenbrough sign positive) (Panel D).

Because of insufficient response to pharmacological therapy, we performed a TASH procedure (transcoronary alcohol septal ablation for hypertrophic cardiomyopathy). There was no pressure gradient in the LVOT left post-procedure, and the patient did clinically well without complaints of dyspnoea.

Multiple LEOPARD syndrome is an autosomal dominant multiple congenital anomaly syndrome, with high penetrance and markedly variable expression. It was originally described by Gorlin as multiple lentigines syndrome. It is also known as cardiocutaneous syndrome, Moynahan syndrome, lentiginosis profuse, and progressive cardiomyopathic lentiginosis. Apart from pulmonary valve stenosis, HOCM is a common feature of this syndrome and it may progress with age or present later in life than the other clinical findings. The most plausible explanation for the pathogenesis of the syndrome is an abnormality of the neural crest cell. The cells derived from the neural crest form spinal and autonomic ganglion cells, Schwann cells of peripheral nerves, as well as sympathetic terminations in the cardiac ventricles. Neural crest cells also give rise to melanocytes, thereby explaining the associated lentigines.

The underlying genetic defect associated with the development of the syndrome has been located on chromosome 12 (gene map locus 12q24.1), and the responsible gene is *PTPN11* (protein tyrosine phosphatise non-receptor type 11), which codes for non-receptor protein tyrosine phosphatise, SHP2. Mutations in the same gene are known to lead to a number of congenital heart defects, among them Noonan syndrome, cardiomyopathic lentiginosis, and LEOPARD syndrome. Different heart defects correlate with different locations of mutations within the *PTPN11* gene. The only son of our patient also demonstrated features of the LEOPARD syndrome, without documentation of cardiac involvement so far.

See supplementary movies available at *European Heart Journal* online.

Panel A. Multiple lentigines.

Panel B. Electrocardiogram showing left-axis deviation, left anterior hemiblock, ST-segment abnormalities, and T-wave inversions.

Panel C. Echocardiographic image of hypertrophic obstructive cardiomyopathy with thickened interventricular septum and systolic anterior motion of the mitral valve leaflets. The anterior mitral valve leaflet obstructing the left ventricular outflow tract is indicated with a white arrow.

Panel D. Haemodynamic tracings with intraventricular pressure gradient and positive Brockenbrough sign (post-extra systolic aggravation of obstruction with augmentation of the intraventricular pressure gradient and lowering of the aortic pressure), indicated in the figure with an asterisk.