Meta-Analysis of the Quantitative Relation Between Pulse Pressure and Mean Arterial Pressure and Cardiovascular Risk in Patients With Diabetes Mellitus

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Results of epidemiologic studies that investigated the significance of pulse pressure (PP) and mean arterial pressure (MAP) in terms of risk of cardiovascular disease (CVD) in patients with diabetes mellitus are inconsistent. We performed a quantitative meta-analysis to estimate CVD risk in relation to PP or MAP. Electronic literature search was conducted for prospective studies providing data on CVD risk for an increment in baseline MAP or PP in patients with diabetes mellitus. The pooled CVD risk for a 10-mm Hg increase in each blood pressure (BP) index was estimated with a random-effects model. There were 17 eligible studies consisting of 52,647 patients and 5,112 CVD cases. The pooled relative risk (95% confidence interval) of CVD for an increment of 10 mm Hg was 1.10 (1.04 to 1.16) for PP and 1.09 (0.98 to 1.21) for MAP. Significant between-study heterogeneity was observed (I^2 [p value]; 76.5% [p <0.001] for PP, 67.8% [p = 0.005] for MAP). In studies concurrently investigating CVD risk for the 4 indexes (i.e., PP, MAP, systolic BP, and diastolic BP), the pooled relative risk (95% confidence interval) was 1.17 (1.09 to 1.26) for PP, 1.11 (1.06 to 1.15) for MAP, 1.14 (1.06 to 1.22) for systolic BP, and 1.06 (0.94 to 1.19) for diastolic BP. In conclusion, the current meta-analysis suggested that PP was the strongest indicator among the 4 commonly used BP indexes. However, the large heterogeneity urged cautious interpretation of the study results. © 2014 Elsevier Inc. All rights reserved. **(Am J Cardiol 2014;113:1058–1065)**

There has been a well-established relation between blood pressure (BP), in particular systolic BP, and risk of cardiovascular disease (CVD) in patients with diabetes mellitus (DM) as well as in the general population. Recently, attention has been paid to 2 other indexes, mean arterial pressure (MAP) and pulse pressure (PP), whose components include both systolic and diastolic BP; MAP is calculated as1/3 × SBP + 2/3 × DBP, and PP is calculated as SBP − DBP, where SBP denotes systolic BP and DBP denotes diastolic BP. In the general population, compared with systolic and diastolic BP, PP has a lower predictive value for CVD whereas MAP has a comparable or greater predictive value.[1] However, the relative magnitude among the BP indexes in terms of CVD risk is hypothesized to be specific for DM, considering that in subjects at high risk for CVD, systolic BP is higher and diastolic BP is lower (i.e., PP, but not necessarily MAP, is enlarged) in those with DM compared with those without DM.[2] However, results of epidemiologic studies that investigated the significance of PP and MAP in terms of CVD risk in patients with DM are inconsistent. The aim of this meta-analysis is to comprehensively estimate CVD risk in relation to PP or MAP based on previously published prospective studies.

Methods

An electronic literature search using MEDLINE (from January 1, 1950 to April 2, 2013) and EMBASE (from January 1, 1974 to April 2, 2013) was conducted for studies providing data on future CVD risk in relation to baseline MAP or PP values in patients with DM. Study keywords were text words related to DM, MAP, PP, and CVD or thesaurus terms registered in MEDLINE (MeSH) or EMBASE (Emtree) related to DM (i.e., "diabetes mellitus, type 2" OR "diabetes mellitus" OR "diabetes mellitus, type 1" [in MeSH] and "insulin-dependent diabetes mellitus" OR "juvenile diabetes mellitus" OR "diabetes mellitus" OR "maturity-onset diabetes mellitus" OR "non–insulin-dependent diabetes mellitus" [in Emtree]) and CVD (i.e., "coronary disease" OR "coronary artery disease" OR "myocardial ischemia" OR "myocardial infarction" OR "cerebrovascular disorders" OR "brain ischemia" OR "stroke" OR "intracranial embolism and

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See page 1064 for disclosure information.

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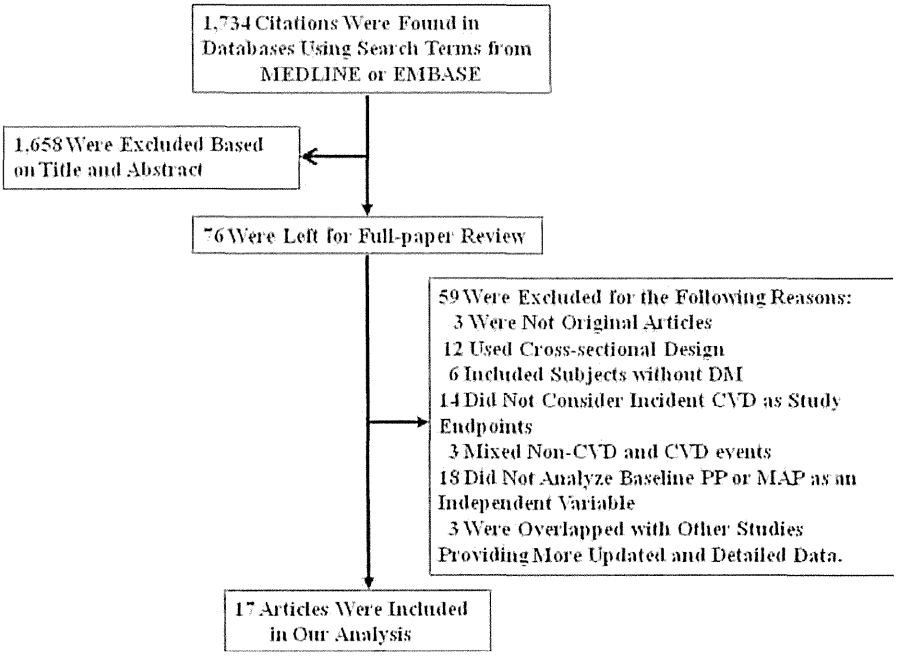

Figure 1. Flow chart of literature search for eligible studies.

thrombosis" OR "intracranial hemorrhages" OR "brain infarction" OR "cerebral infarction" OR "subarachnoid hemorrhage" [in MeSH] and "acute coronary syndrome" OR "ischemic heart disease" OR "acute heart infarction" OR "heart infarction" OR "stroke" OR "brain ischemia" OR "subarachnoid hemorrhage" OR "brain hemorrhage" OR "transient ischemic attack" OR "brain ventricle hemorrhage" OR "cerebellum hemorrhage" OR "cerebrovascular disease" OR "cardiovascular disease" [in Emtree]). The 3 key concepts (i.e., DM, MAP or PP, or CVD) were combined using the Boolean operator "AND" after combining MAP and PP using the Boolean operator "OR." Manual searches for relevant reports were added from examination of reference lists of the identified reports. No language restriction was imposed. Studies were included if (1) all participants had diabetes regardless of the type of diabetes; (2) incident CVDs were prospectively followed-up; (3) baseline values at cohort entry were presented for either PP or MAP or both PP and MAP; and (4) data on the relative risk (RR) of CVD for an increment in PP or MAP at cohort entry were provided.

The CVD end points included CVDs, coronary heart diseases (CHDs), and stroke that were symptomatic. Studies that investigated CHD or stroke apart from CVDs were included. Studies considering only fatal CVD as the study end point were also included. In studies that not only included data on risk of fatal CVD but also provided data on both fatal and nonfatal CVD, priority was given to data on risk of outcome that included both fatal and nonfatal events. If studies separately investigated fatal and nonfatal CVD, we chose the data on fatal CVD risk because it was the more serious event. Studies regarding peripheral vascular disease as a part of total CVD were also included. However, studies that mixed microvascular diseases (e.g., end-stage renal disease) and CVDs as study end points were excluded because these 2 end points involved entirely different concepts.

Two authors (SK and HS) independently extracted data, and discrepancies were solved by discussion. Data extracted from each study included the following: geographic region, type of DM (type 1, type 2, or nonspecified), definition of CVD outcomes, methods for ascertainment of CVD, mean age, gender, mean systolic BP, mean diastolic BP, proportion of patients taking antihypertensive drugs, duration of DM, follow-up periods, whether patients who already had CVD were excluded (yes or no), study covariates, and risk estimates for CVD. If the study reported multiple RRs for the same increment of BP, the most adjusted RR was used. For 1 study, in which the most adjusted RR could not be specified,[3] we chose the RR adjusted for age, gender, and antihypertensive drugs. Study quality was assessed by modifying the Newcastle-Ottawa Quality Assessment Scale[4] so that it was applicable to our theme. In summary, the Newcastle-Ottawa Quality Assessment Scale consists of 3 major items: S (selection, 3 questions), C (comparability, 2 questions), and O (outcome, 3 questions). For each "yes" answer, 1 point was awarded.

Data syntheses were separated by each combination of outcomes (i.e., CVD, CHD, or stroke) and by the BP indexes (i.e., PP, MAP, systolic BP, and diastolic BP). The RRs were transformed into natural logarithms—ln(RR)—and standardized into those for a 10-mm Hg increment. Each standardized ln(RR) was pooled with a random-effects model[5] and the final RR was calculated by exponentiation of the pooled ln(RR). For PP and MAP, the data syntheses were conducted by each combination of outcomes (i.e., CVD, CHD, or stroke). Between-study heterogeneity was assessed by I^2.[6]

We compared the magnitude of CVD risk in relation to an increment in any 2 of the 4 BP indexes, limiting the analysis to studies that provided data on the RR for systolic

Table 1
Characteristics of the 17 included studies in this meta-analysis

First Author (Year)	Country	Included Nonfatal Event	Type of DM	F/U Duration (Yrs)	Complete F/U	Mean Age (Yrs)	% of Men	DM Duration (Yrs)	No. of Patients	No. of Cases			Mean Systolic BP (mm Hg)	Mean Diastolic BP (mm Hg)	CVD (IHD) Prevalence (%)	Anti-HT Medication (%)*	CVD Assessment
										CVD	CHD	Stroke					
Nazimek-Siewniak (2002)[23]	PL	No	2	14	No	56	42	0	1,815				140	84	0	55	M
Schram (2002)[22]	NL	Yes	2	8.6	No	66	43	0	208	34			146	84	26	41	R
Schram (2003)[21]	NL	No	1	7.4	Yes	33	51	13	2,565	163			121	75	10	10	M
Nakano (2004)[20]	JP	No	2	7.2	Yes	54	64	7.5	364	50			125	73	0	39	M
Cockcroft (2005)[19]	UK	No	2	4.0	Yes	66	54	8.8	2,911		574	168	145	82	ND	ND	R
Nakano (2005)[18]	JP	No	2	8.3	Yes	46	69	6.7	228		19	20	122	74	0	ND	M
Ronnback (2006)[3]	FI	Yes	2	9.5	Yes	69	46	6.3	1,294	332			149	83	32	51	R
Zoppini (2007)[17]	IT	Yes	2	10	No	66	45	12	1,128	146	68	42	155	87	ND	ND	R
Tropeano (2008)[16]	FR	Yes	2	0.8	Yes	64	58	9.0	9,379	632			160	88	19	100	M
Kengne (2009)[15]	†	No	2	4.3	Yes	66	58	7.0	11,140	1,000	559	433	145	81	32	69	R
Nilsson (2009)[14]	SWE	No	2	5.6	Yes	63	55	8.0	11,128	1,728	1,175	699	148	82	0	60	R
Hadaegh (2010)[13]	IR	No	1/2	8.4	Yes	54	45	ND	828	134			130	81	0	0	S/M
van Hateren (2010)[12]	NL	No	2	9.8	No												M
60–75 yrs						69	41	6.0	555	114			158	85	37	50	
>75 yrs						80	36	8.0	326	83			156	82	46	60	
Gordin (2011)[11]	FI	Yes	1	5.3	No	39	52	22	4,509	269			134	79	9.0	38	M
Hsieh (2012)[10]	TW	No	2	5.6	Yes	64	57	ND	2,161	25			135	78	ND	79	R
Ruggenenti (2012)[9]	IT	Yes	2	9.1	Yes	62	53	6.2	1,208	189			151	87	4.3	55	M/R
Theilade (2012)[8]	DE	Yes	1	8.0	No	44	57	28	900	213			139	79	ND	ND	R

DE = Denmark; FI = Finland; FR = France; F/U = follow-up; HT = hypertension; IHD = ischemic heart disease; IR = Iran; IT = Italy; JP = Japan; M = medical record; ND = no data; NL = Netherlands; PL = Poland; R = registry; S = self-report or questionnaire; SWE = Sweden; TW = Taiwan; UK = United Kingdom.

* Proportion of patients taking antihypertensive drugs.

† Consisting of multiple countries.

Table 2
Details of covariates considered in each included study in this meta-analysis

First Author (Year)	Covariates
Nazimek-Sieweniak (2002)[23]	Gender, duration of DM, FPG, TC, TG, BMI, and (previous CVD)
Schram (2002)[22]	Age, gender, MAP, and HT medication
Schram (2003)[21]	Age, gender, HbA_{1c}, duration of DM, TC, HDL, LDL, TG, BMI, WHR, smoking, and HT medication
Nakano (2004)[20]	Age, duration of DM, Cre, systolic BP, nocturnal fall in systolic BP, and (previous CVD)
Cockcroft (2005)[19]	Age, gender, smoking, and TC/HDL
Nakano (2005)[18]	Age, systolic BP, duration of DM, Cre, TC/HDL, nocturnal fall in systolic BP, and (previous CVD)
Ronnback (2006)[3]	Age, gender, previous CVD, duration of DM, smoking, and HDL
Zoppini (2007)[17]	Age, gender, duration of DM, BMI, FPG, smoking, DM medication, and PP variation
Tropeano (2008)[16]	Age, gender, neuropathy, CHF, HbA_{1c}, smoking, WC, and HT medication
Kengne (2009)[15]	Age and gender
Nilsson (2009)[14]	Age, gender, duration of DM, HbA_{1c}, BMI, smoking, microalbuminuria, medication for HT, HL, and DM, MAP, and (previous CVD)
Hadaegh (2010)[13]	Age, gender, FPG, WHR, FH of CVD, TC, smoking, aspirin, (previous CVD), and (HT medication)
van Hateren (2010)[12]	Age, gender, BMI, duration of DM, Cre, TC/HDL, previous CVD, albuminuria, and medication for HL and HT
Gordin (2011)[11]	Age, gender, HbA_{1c}, TC, eGFR, smoking, and HT medication
Hsieh (2012)[10]	Age, gender, systolic BP, diastolic BP, HbA_{1c}, FPG, BMI, TC, TG, HDL, LDL, Cre, eGFR, and ACR
Ruggenenti (2012)[9]	Age, gender, FH of CVD, smoking, BMI, HbA_{1c}, LDL/HDL, TG, Cre, UAE, uric acid, and medication for HL
Theilade (2012)[8]	Age, gender, HbA_{1c}, TC, diastolic BP, smoking, previous CVD, Cre, and nephropathy

"(Previous CVD)" means that subjects who had CVD were excluded from the study. "(HT medication)" indicates that subjects who were taking antihypertensive drugs were excluded from the study.

ACR = albumin/creatinine ratio; BMI = body mass index; CHF = chronic heart failure; Cre = creatinine; eGFR = estimated glomerular filtration rate; FH = family history; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein cholesterol; HL = hyperlipidemia; HT = hypertension; LDL = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; UAE = urinary albumin excretion rate; WC = waist circumference; WHR = waist/hip ratio.

Table 3
Study quality assessment according to the modified Newcastle-Ottawa Quality Assessment Scale* (NOS)

First Author (Year)	S1	S2	S3	C1	C2	O1	O2	O3	†Score
Nazimek-Sieweniak (2002)[23]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	7
Schram (2002)[22]	Yes	Yes	No	Yes	No	Yes	Yes	No	5
Schram (2003)[21]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	7
Nakano (2004)[20]	No	Yes	Yes	No	No	Yes	Yes	Yes	5
Cockcroft (2005)[19]	Yes	Yes	No	No	No	Yes	No	Yes	4
Nakano (2005)[18]	No	Yes	Yes	No	No	Yes	Yes	Yes	5
Ronnback (2006)[3]	No	Yes	No	No	No	Yes	Yes	Yes	4
Zoppini (2007)[17]	Yes	Yes	No	No	Yes	Yes	Yes	No	5
Tropeano (2008)[16]	No	Yes	No	Yes	No	Yes	No	Yes	4
Kengne (2009)[15]	No	Yes	No	No	No	Yes	Yes	Yes	4
Nilsson (2009)[14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Hadaegh (2010)[13]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
van Hateren (2010)[12]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	6
Gordin (2011)[11]	Yes	Yes	No	Yes	Yes	Yes	No	No	5
Hsieh (2012)[10]	Yes	Yes	No	No	Yes	Yes	No	Yes	5
Ruggenenti (2012)[9]	No	Yes	No	No	Yes	Yes	Yes	Yes	5
Theilade (2012)[8]	No	Yes	No	No	Yes	Yes	Yes	No	4

* Newcastle-Ottawa Quality Assessment Scale consists of the following 3 major items: S (selection), C (comparability), and O (outcome). Each question corresponding to the individual item number is as follows: S1. Were participants representative of typical diabetic patients? S2. Was baseline BP assessed by measurement? S3. Did each study demonstrate that participants with CVD were not present at the start of cohort? C1. Did the study control for the presence of hypertension or use of medication for hypertension? C2. Other than the covariate described in C1, did study consider at least 6 of the 11 covariates as indicated in Methods? O1. Were CVD events ascertained by linkage with records such as medical records or registries? O2. Was follow-up period for ascertainment of DM 8 years or more? O3. Did study achieve complete follow-up, including the exclusion of participants who were lost to follow-up from the analysis?

† Each "yes" answer to a question was awarded 1 point. Full score is 8.

BP or diastolic BP and for PP or MAP. For CVD risk in relation to PP or MAP, sensitivity analyses were added by (1) stratifying the included studies by mean age (<60 or ≥60 years) of participants and (2) meta-regression analysis, in which natural logarithms of RR for the 10-mm Hg increment were regressed on mean systolic and diastolic BP.

Publication bias was assessed by 2 formal tests: the Begg-adjusted rank correlation test and Egger's regression

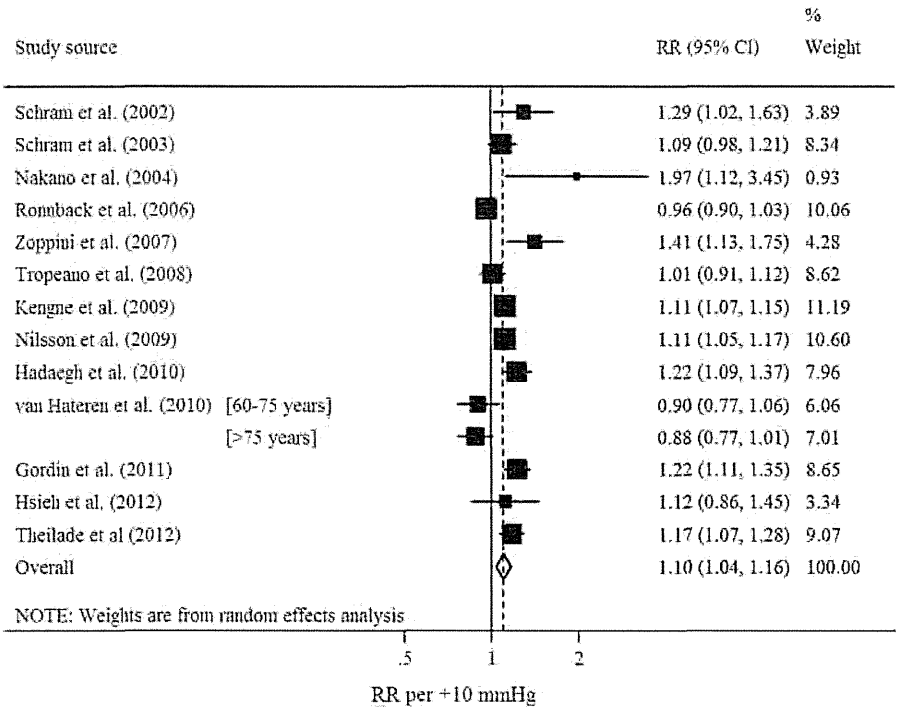

Figure 2. Forest plots of RR with 95% CI of CVD in relation to a 10-mm Hg increment in PP. The RRs in each study and the overall RR are indicated by *squares* and *diamonds*, respectively. *Horizontal lines* indicate the range of 95% CI. *Areas of the square* are proportional to the study weight expressed as the inverse of the square of standard error based on a random-effects model.

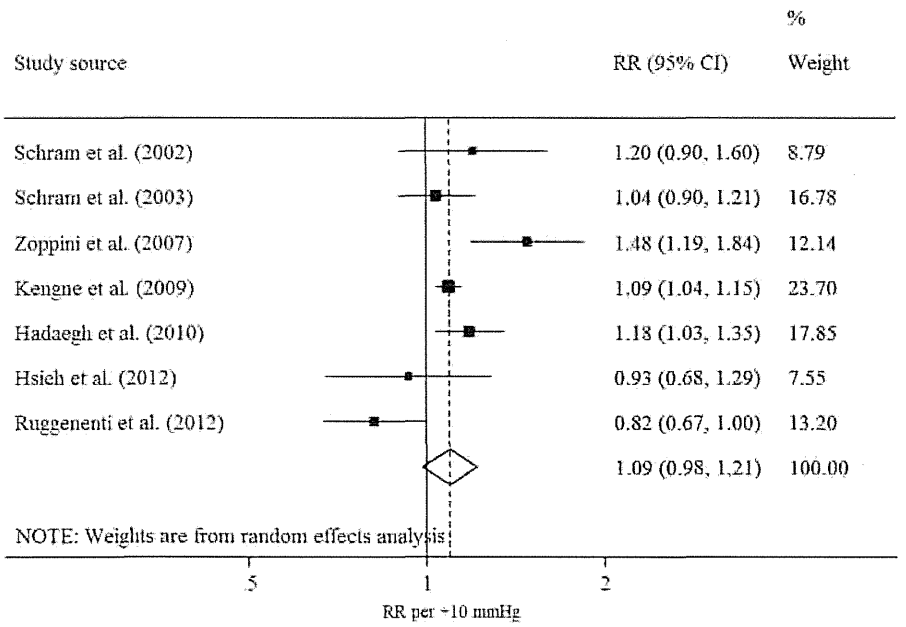

Figure 3. Forest plots of RR with 95% CI of CVD in relation to a 10-mm Hg increment in MAP. The RRs in each study and the overall RR are indicated by *squares* and *diamonds*, respectively. *Horizontal lines* indicate the range of 95% CI. *Areas of the squares* are proportional to the study weight expressed as the inverse of the square of standard error based on a random-effects model.

asymmetry test as well as by visual inspection of a funnel plot. If publication bias was statistically suspected, we tried to adjust the risk estimates for publication bias using the trim-fill method.[7] Data were analyzed using Stata software, version 11 (StataCorp, College Station, Texas). Two-sided p value <0.05 was considered statistically significant.

Results

Of 1,734 reports retrieved from MEDLINE and EMBASE searches, 17 eligible studies[3,8–23] consisting of 52,647 patients with DM were included in this meta-analysis (Figure 1). One study[23] did not describe the number of cases.

Table 4
Assessment of publication bias

Variable	p Value for Begg's Test	Publication Bias Egger's Test	RR (95% CI) Before the Adjustment for Publication Bias	RR (95% CI) After the Adjustment for Publication Bias Using Trim-Fill Method*
PP				
CVD	0.48	0.68	—	—
CHD	0.05	0.07	1.19 (1.08–1.31)	1.14 (1.02–1.27)
Stroke	0.62	0.32	—	—
MAP				
CVD	0.65	0.99	—	—
CHD	†	†	—	—
Stroke	†	†	—	—

* This method includes the assumption that the funnel plot is symmetrical if there is no publication bias, detection of the hypothetically unpublished data causing the funnel plot to be asymmetrical, and recalculation of the pooled risk estimates after filling these data as if they had actually existed.
† Assessment of publication bias was impossible because of limited data.

There were 5,112 CVD cases, 2,395 CHD cases, and 1,362 stroke cases in the remaining 16 studies. Although all but 2 studies[9,23] analyzed PP, only 8 studies[9,10,13,15,17,21–23] analyzed MAP. Two studies[12,13] stratified their analyses into 2 subgroups according to age, but only 1 study[13] also performed the analysis for the total study population.

Table 1 summarizes the characteristics of the 17 included studies. The covariates considered in each study are described in Table 2. Only 1 study[13] excluded patients with DM who took antihypertensive drugs, whereas, of the other 16 studies, 7 studies[11,12,14,16,20–22] included taking medication for hypertension as a covariate. Excluding the covariate related to hypertension, 9 studies[8,10–14,17,21] adjusted CVD risk for ≥6 of the 11 following potential cardiovascular risks factors that we a priori specified: age, gender, smoking, obesity indicators (body mass index, waist circumferences, or waist/hip ratio), duration of DM, systolic BP or MAP value, blood lipid values (total or low-density lipoprotein cholesterol, presence of hyperlipidemia or hyperlipidemia medication, high-density lipoprotein cholesterol, or triglycerides), nephropathy indicators (creatinine level, estimated glomerular filtration rate, urinary albumin excretion rate or presence of nephropathy), previous CVD or presence of chronic heart failure, and blood glucose level (fasting plasma glucose or hemoglobin A_{1c}). Table 3 lists the results of assessment of study quality mainly based on data in Tables 1 and 2. Subjects were considered to reflect typical patients with DM in 10 studies[8,10–14,16,17,21,23] wherein outpatients who were receiving treatment for DM were exclusively recruited. Finally, the mean ± SD quality score was 5.1 ± 1.1 points. We judged the quality of 5 studies[3,8,15,16,19] with a score<5 points as low.

Figures 2 and 3 show forest plots with the 95% confidence interval (CI) of CVD risk in relation to PP and MAP, respectively. There were 13 studies[3,8,10–17,20–22] and 7 studies[9,10,13,15,17,21,22] that analyzed PP and MAP, respectively, and used CVD as an independent outcome. One study[12] stratified the analysis into 2 subgroups according to age but did not present data on CVD risk for the total study population. Therefore, we included the 2 data sets based on the stratified analysis; total number of data on CVD risk in relation to PP was 14. The pooled RR (95% CI) of CVD for the 10-mm Hg incremental increase was positive both for PP (1.10 [1.04 to 1.16], p = 0.001) and MAP (1.09 [0.98 to 1.21], p = 0.10). Between-study heterogeneity was significant in both associations with CVD risk (I^2; 76.5% [p <0.001] for PP and 67.8% [p = 0.005] for MAP). Regarding other end points, the pooled RR (95% CI) of 5 studies[14,15,17–19] that investigated the risk of CHD and stroke for an increment of 10 mm Hg in PP was significant (1.19 [1.08 to 1.31] for CHD and 1.18 [1.06 to 1.31] for stroke), although there was a significant heterogeneity (I^2; 66.6% [p = 0.02] for CHD and 59.1% [p = 0.04] for stroke). Only 2 studies[15,23] investigated the RR for the 10-mm Hg increment in MAP with regard to CHD and stroke. The pooled RR (95% CI) was 1.13 (1.07 to 1.20) for CHD and 1.12 (1.05 to 1.20) for stroke. Study heterogeneity was not significant due to limited data (I^2; 17.3% [p = 0.27] for CHD and 59.7% [p = 0.12] for CHD).

Six studies[10,13,15,17,21,22] investigated CVD risk in relation to all of the 4 BP indexes (i.e., PP, MAP, systolic BP, and diastolic BP) concurrently. The RR (95% CI) of CVD for a 10-mm Hg increment was 1.17 (1.09 to 1.26) for PP, 1.11 (1.06 to 1.15) for MAP, 1.14 (1.06 to 1.22) for systolic BP, and 1.06 (0.94 to 1.19) for diastolic BP. Nine studies[3,10,12,13,15,17,20–22] assessed CVD risk for the increase in both PP and systolic BP. The pooled RR (95% CI) for a 10-mm Hg increment was 1.10 (1.01 to 1.20) for PP and 1.05 (0.97 to 1.13) for systolic BP. Similarly, when our analysis was limited to the 8 studies[3,10,12,13,15,17,21,22] that analyzed PP and diastolic BP concurrently, CVD risk was positive for PP but not for diastolic BP (pooled RR [95% CI] for the increment of 10 mm Hg; 1.08 [0.996 to 1.18] for PP and 0.98 [0.88 to 1.09] for diastolic BP).

With regard to CVD risk in relation to PP, a tendency for a strong association was observed in studies of subjects with a mean age of <60 years (RR [95% CI], 1.18 [1.12 to 1.24]) compared with those with a mean age of ≥60 years (RR [95% CI], 1.07 [0.999 to 1.15]). When mean systolic BP and diastolic BP were entered as independent variables, mean systolic BP significantly weakened the association between PP and CVD risk (β coefficient for 10-mm Hg increment in systolic BP = −0.12, p = 0.04), whereas mean diastolic BP did not influence it (β coefficient for 10-mm Hg increment in diastolic BP = 0.25, p = 0.18).

With regard to CVD risk in relation to MAP, there was no difference in the magnitude of CVD according to the mean age of the study population (RR [95% CI], 1.12 [1.01 to 1.23] for mean age <60 years, 1.12 [0.97 to 1.30] for mean age ≥60 years). In addition, the CVD risk in relation to MAP was not modified by either mean systolic BP (β coefficient for 10-mm Hg increment in diastolic BP = −0.06, p = 0.23) or mean diastolic BP (β coefficient for 10-mm Hg increment in diastolic BP = 0.42, p = 0.07).

Results of the probability of publication bias statistically assessed by several outcomes suggested a suspicion of publication bias for the association between the incremental increase in PP and CHD based on Begg's test (p = 0.05; Table 4). After adjustment for publication bias, the RR for CHD risk in relation to a 10-mm Hg increment in PP was deflated by approximately 5%, although the general conclusion was not changed. Publication bias was not statistically

detected for the risk of other outcomes (i.e., CVD and stroke) in relation to PP or for any outcomes in relation to MAP.

Discussion

The present meta-analysis indicated that PP and MAP were positively associated with future CVD risk in patients with DM, although the association between MAP and CVD risk was not significant, partly due to the limited number of studies. When analysis was limited to studies that investigated CVD risk in relation to the 4 BP indexes (i.e., PP, MAP, systolic BP, and diastolic BP), PP was shown to have a larger RR for a +10-mm Hg increment than the other 3 indexes, indicating that PP might be the most accurate factor for estimating CVD risk in patients with DM among the well-known BP indexes. In addition, the meta-regression analysis indicated that the association between PP and CVD risk was strengthened by a decreasing mean systolic BP in the study population. PP was suggested to be a strong predictor of CVD beyond systolic BP.

In the general population, the relationship between PP and coronary disease risk was gradually strengthened with increasing age.[24] However, the present stratified analysis indicated that in studies of subjects with a mean age of <60 years rather than ≥60 years, the RR was high for the +10-mm Hg increment in PP. It is possible that patients with DM resemble older subjects regarding the predictability of PP for CVD because the aging of blood vessels begins at an earlier age in patients with DM. This possibility could be explained by the pathophysiological finding that the formation of advanced glycation end product, which played an important role in the development of atherosclerosis, was promoted by both hyperglycemia and aging.[25] It is of note that studies of subjects with a mean age of ≥60 years revealed a nonsignificant RR of CVD for the 10-mm Hg increment in PP. One possible speculation was that the relative contribution of BP to CVD risk would have been diluted because the elderly subjects, particularly if they had DM, had a large number of cardiovascular risk factors other than hypertension.

It was also of note that the association between systolic BP and future CVD risk was nonsignificant from the meta-analysis of studies that presented data on CVD risk for both systolic BP and PP, which was paradoxical to the well-known relationship between systolic BP and CVD. The possible reason for the present result was that the DM population has a generally greater prevalence of taking antihypertensive drugs compared with the non-DM population, as was the case with the included studies in this meta-analysis. Excessive lowering of diastolic BP, which inevitably accompanies the control of BP, mainly systolic BP, by medication could play a role in the elevated risk of CVD.[26] Another explanation was that patients having low BP values due to heart failure, which was more prevalent in patients with DM than without DM,[27] could have a high incidence rate of CVD.[28] In addition, patients with DM had increased BP variability compared with those without DM.[10] The within-person fluctuations of BP, particularly in patients with DM, could have diluted the association of BP with CVD risk.

Several limitations should be addressed. First, the large between-study heterogeneity in the RR for CVD as was indicated by I^2 urged us to interpret the study results with caution. Second, we had to assume linearity of the association between BP values and CVD risk to make it possible to compare the strength of the association between any 2 BP indexes. Third, this meta-analysis could not accurately indicate 3 or more dimensional relations among 2 or more BP indexes and CVD risk although meta-regression analyses were conducted by entering baseline systolic BP or diastolic BP as explanatory variables. Fourth, the covariates for adjusting the CVD risk varied among studies, which might bias the results. Fifth, we could not discuss differences according to gender because no study analyzed the association between BP indexes and CVD risk by gender. Sixth, the CVD events in the follow-up periods could be either primary or recurrent because most of the included studies did not exclude patients who had already had a history of CVD. The present meta-analysis could not determine whether BP was specifically associated with primary CVD or recurrent CVD as compared with its clinical significance because no study stratified the CVD events into primary and recurrent CVD.

Lastly, BP change during the follow-up period for ascertaining incident CVD could modify the relation between baseline BP and CVD risk. Only 1 study[29] investigated the risk of CVD, myocardial infarction, and stroke in relation to mean MAP during the follow-up period. This method could have more accurately estimated CVD risk in relation to high BP values than using baseline values. However, we unfortunately had to exclude this study in this meta-analysis because the methodologic features were critically different from those in the included studies in the current meta-analysis.

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ORIGINAL ARTICLE

Fasting glucose and HbA1c levels as risk factors for the development of hypertension in Japanese individuals: Toranomon hospital health management center study 16 (TOPICS 16)

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We investigated the effect of elevated concentrations of fasting plasma glucose (FPG) or hemoglobin A1c (HbA1c) on the risk of development of hypertension among apparently healthy Japanese. Studied were 9584 individuals without known diabetes and hypertension. During a 5-year follow-up period, 1098 individuals developed hypertension. Elevated concentrations of FPG, rather than of HbA1c, were significantly predictive of future hypertension. Compared with the lowest quartile category of FPG (<4.9 mmol l^{-1}), the second (4.9– <5.2 mmol l^{-1}), third (5.2– <5.6 mmol l^{-1}) and highest ($\geqslant 5.6$ mmol l^{-1}) quartile categories had age-, sex- and body mass index-adjusted odds ratios (95% confidence interval) of 1.35 (1.10, 1.66), 1.39 (1.13, 1.71) and 1.85 (1.51, 2.28) for hypertension, respectively. In the highest quartile of FPG, the multivariate-adjusted OR was 1.37 (1.10, 1.70) compared with the lowest quartile. Results of these adjusted models showed no significant association across quartile categories of HbA1c concentrations and an increased risk of developing hypertension. The joint effect of hyperglycemia and overweight, older age or prehypertension resulted in further elevated ORs for hypertension than the absence of such an association. Higher FPG levels rather than HbA1c were strongly predictive of future hypertension among Japanese. Hyperglycemia along with older age, overweight and prehypertension contributed to identifying individuals at increased risk of developing hypertension.

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INTRODUCTION

A review showed that high blood pressure was observed in over two-thirds of patients with type 2 diabetes and that its development would coincide with the development of hyperglycemia.[1] Possible mechanisms underlying the association would include insulin resistance, hyperinsulinemia and the excitatory effect of hyperglycemia itself.[1,2] Although elevated concentrations of fasting glucose or hemoglobin A1c (HbA1c) were reported to be predictive of the development of hypertension,[3–14] a question exists as to whether there is an association between elevated fasting plasma glucose (FPG) levels or HbA1c within normal range but below prediabetic ranges and an increased risk of hypertension. Additionally, to date few studies have directly compared the prognostic abilities of HbA1c and glucose for hypertension among individuals without known diabetes.[11] Two studies observed a positive association between elevated HbA1c concentrations below the diagnostic threshold for diabetes ($<6.5\%$) and an increased risk of hypertension, while the association was attenuated after adjustment for measures of adiposity, suggesting an important association between adiposity and hyperglycemia with the risk of hypertension.[10,11] In addition to the predictive role of each glycemic measurement for the development of hypertension, it also would be important to investigate the separate and combined effect of hyperglycemia and common risk factors for hypertension, such as older age, overweight, obesity and prehypertension.[15–17] Therefore, our study, which included participants from the Toranomon Hospital Health Management Center Study, assessed whether glycemic markers could help detect apparently healthy Japanese individuals at increased risk for the development of hypertension.

SUBJECTS AND METHODS

Study participants

The Toranomon Hospital Health Management Center Study included a cohort consisting mainly of apparently healthy government employees who underwent annual examinations for health screening in Tokyo, Japan. At the time of each annual physical examination, anthropometric measurements were taken, biochemical tests were performed and participants were interviewed using the standard questionnaires that gathered information on demographic characteristics, medical history and health-related habits. We investigated 12 357 individuals who underwent a baseline examination during the period from 1997 to 2007 and provided data on blood pressure measurements, a self-reported history of medical treatment for hypertension or the use of antihypertensive medication at a re-examination 5 years after the baseline examination. Routine health checkups are very common in Japan, because the Japanese government and companies encourage people to have periodic health examinations. Among the 12 357 individuals, we excluded individuals with hypertension at the baseline examination (indicated by systolic blood pressure (SBP) $\geqslant 140$ mm Hg, diastolic blood pressure (DBP) $\geqslant 90$ mm Hg or a self-reported history of treatment for hypertension ($n=2456$)), individuals

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with a self-reported history of clinician-diagnosed diabetes ($n=283$) or with missing data on baseline characteristics ($n=159$). Subsequently, 9584 individuals (2970 women and 6614 men) aged 20–80 years were included in the current analysis. The study protocol followed the Japanese Government's Ethical Guidelines Regarding Epidemiological Studies in accordance with the Declaration of Helsinki and was reviewed by the Institutional Review Board at Toranomon Hospital.

Clinical and other measurements

Height and weight were measured and body mass index (BMI) (kg m^{-2}) was calculated. At the time of the health examinations, after a brief period of rest, SBP and DBP were measured in either arm using a sphygmomanometer (Omron Corporation, Kyoto, Japan) with the participant in a sitting position. Blood pressure was measured once in most participants, but up to three measurements at 1–2-min intervals were made in participants who had hypertensive or prehypertensive SBP and DBP values. The lowest reading was used in the analysis that assessed the incidence of hypertension. Smoking habit and parental history of hypertension were assessed by a questionnaire, as was self-reported history of hypertension or diabetes. Blood samples were collected after an overnight fast, and measurements were made using an automatic clinical chemistry analyzer (Hitachi, LABOSPECT 008, Tokyo, Japan). Blood glucose was measured by enzymatic methods, and HbA1c was assessed by high-performance liquid chromatography. The value for HbA1c was estimated as the National Glycohemoglobin Standardization Program value (%) calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society (%)) × 1.02+0.25%.[18]

Statistical analysis

Logistic regression analysis was performed using FPG or HbA1c as a continuous variable (1-s.d. increment) or quartile (Q) categories for the development of hypertension; odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. To investigate the impact of factors that influenced the association between the glycemic markers and hypertension, we analyzed data using models with the following adjustments: age and sex (model 1), model 1+BMI (model 2), and model 2+SBP (model 3). The multivariable model (model 4) included age, sex, BMI, SBP, parental history of hypertension, smoking habit (never, former, current), log-transformed triglycerides, log-transformed γ-glutamyltransferase and uric acid.[15–17,19,20] For sensitivity analysis, we analyzed data when incident cases of hypertension were indicated by only a self-reported history of hypertension. To investigate a joint association of elevated glycemic markers and older age, overweight or prehypertension, we stratified participants according to age (20–46 or 47–80 years), BMI (BMI $\geqslant$ 23.0 kg m^{-2} or $<$ 23.0 kg m^{-2})[21] and prehypertension (SBP $\geqslant$ 120 mm Hg or DBP $\geqslant$ 80 mm Hg) or normotension (SBP $<$ 120 mm Hg and DBP $<$ 80 mm Hg). Participants were categorized by groups according to median FPG or HbA1c values.

RESULTS

We documented 1098 incident cases of hypertension that were identified by measured SBP $\geqslant$ 140 mm Hg, measured DBP $\geqslant$ 90 mm Hg or a self-reported history of treatment for hypertension at 5 years after the baseline examinations (Table 1). Individuals who later developed hypertension were older and more likely to have a parental history of hypertension, higher BMI or higher concentrations of FPG at the baseline examination compared with those who did not develop hypertension ($P<0.001$).

We observed a significant positive association between a 1-s.d. increment in FPG or HbA1c values for incident hypertension with an OR 1.24 (95% CI 1.17, 1.30) or OR 1.15 (95% CI 1.09, 1.22), respectively, in the unadjusted model (Table 2). Even after adjustment using variables included in the multivariate model, FPG concentrations were significantly predictive of future hypertension. On the other hand, HbA1c concentrations did not have predictive value after adjustment for age, sex and BMI in model 2. Using results for incident cases of hypertension indicated by a self-reported history of hypertension alone ($n=278$), we also confirmed the higher predictive value of FPG rather than HbA1c concentrations (Table 2b). As we observed that older age influenced the association of HbA1c and the development of hypertension, we stratified participants into two age groups (aged $<$ 47 years ($n=4679$) or aged $\geqslant$ 47 years ($n=4905$)) and further calculated ORs. We found that HbA1c was more predictive of the development of hypertension in younger participants (crude OR by 1 unit (%) increment of HbA1c: 1.45; 95% CI 1.19, 1.77) than in the older participants (OR 1.20; 95% CI 1.04, 1.39).

Table 3 shows ORs for the development of hypertension across quartiles of FPG or HbA1c concentrations. Compared with the lowest quartile (Q) of FPG (Q1: $<$ 4.9 mmol l^{-1}), ORs for hypertension were significantly elevated in the second (Q2: 4.9– $<$ 5.2 mmol l^{-1}), third (Q3: 5.2– $<$ 5.6 mmol l^{-1}) and fourth quartile (Q4: $\geqslant$ 5.6 mmol l^{-1}) categories (age- and sex-adjusted OR (95% CI) 1.53 (1.25, 1.88), 1.69 (1.38, 2.07) and 2.62 (2.16, 3.18), respectively). The ORs in the Q2–Q3 categories were significantly elevated with an adjustment for BMI in model 2 but were

Table 1. Characteristics of the total study participants at the baseline examination and according to incidence of hypertension 5 years later

	Total (n = 9584)	*Incidence of hypertension*		P-*value*[a]
		NO (n = 8486)	*YES (n = 1098)*	
Female sex	2970 (31.0)	2677 (31.5)	293 (26.7)	0.001
Age, years	47.4 ± 8.3	47.1 ± 8.1	49.8 ± 8.7	< 0.001
Parental history of hypertension, yes	3115 (32.5)	2683 (31.6)	432 (39.3)	< 0.001
Smoking habit				< 0.001
Never	5227 (54.5)	4691 (55.3)	536 (48.8)	—
Former	1898 (19.8)	1625 (19.1)	273 (24.9)	—
Current	2459 (25.7)	2170 (25.6)	289 (26.3)	—
Body mass index, kg m^{-2}	22.6 ± 2.8	22.4 (2.8)	23.7 (2.8)	< 0.001
Systolic blood pressure, mm Hg	119 ± 12	118 ± 12	128 ± 8	< 0.001
Diastolic blood pressure, mm Hg	73 ± 8	72 ± 8	80 ± 6	< 0.001
Uric acid, μmol l^{-1}	328.3 ± 81.4	326.4 ± 81.1	343.4 ± 82.9	< 0.001
Triglycerides, mmol l^{-1}	1.02 (0.72, 1.48)	0.99 (0.71, 1.45)	1.16 (0.84, 1.66)	< 0.001
γ-Glutamyltransferase, U l^{-1}	30 (19, 53)	29 (19, 51)	40 (23, 71)	< 0.001
Fasting plasma glucose, mmol l^{-1}	5.27 ± 0.66	5.24 ± 0.64	5.44 ± 0.78	< 0.001
HbA1c, %	5.27 ± 0.46	5.26 ± 0.45	5.34 ± 0.53	< 0.001

Abbreviation: HbA1c, hemoglobin A1c. Data are n (%), mean ± s.d. or median (25th, 75th). [a]*P* values were tested by *t*-test, median test or χ^2 test between cases with and without hypertension.

Table 2. Odds ratios (95% CIs) for the development of hypertension at 5 years after baseline examination by 1-s.d. increments in fasting plasma glucose (FPG) or HbA1c concentrations

	FPG		*HbA1c*	
	OR (95% CI)	P-*value*	*OR (95% CI)*	P-*value*
(a) Incident cases of hypertension indicated by SBP ⩾ 140 mm Hg, DBP ⩾ 90 mm Hg or self-reported hypertension				
Unadjusted model	1.24 (1.17, 1.30)	< 0.001	1.15 (1.09, 1.22)	< 0.001
Adjusted model 1, age and sex	1.20 (1.13, 1.26)	< 0.001	1.09 (1.03, 1.15)	0.003
Adjusted model 2, age, sex and BMI	1.13 (1.08, 1.19)	< 0.001	1.03 (0.97, 1.10)	0.266
Adjusted model 3, age, sex, BMI and SBP	1.10 (1.04, 1.16)	0.001	1.06 (0.995, 1.12)	0.070
Adjusted model 4, multivariate	1.08 (1.02, 1.15)	0.008	1.05 (0.99, 1.12)	0.127
(b) Incident cases of hypertension indicated by self-reported hypertension alone				
Unadjusted model	1.17 (1.10, 1.26)	< 0.001	1.18 (1.09, 1.28)	< 0.001
Adjusted model 1, age and sex	1.14 (1.06, 1.23)	< 0.001	1.09 (0.99, 1.20)	0.075
Adjusted model 2, age, sex and BMI	1.11 (1.02, 1.20)	0.016	1.05 (0.95, 1.16)	0.340
Adjusted model 3, age, sex, BMI and SBP	1.09 (0.995, 1.19)	0.063	1.06 (0.96, 1.18)	0.235
Adjusted model 4, multivariate	1.09 (0.99, 1.20)	0.066	1.06 (0.96, 1.18)	0.244

Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; OR, odds ratio; SBP, systolic blood pressure. Model 1: ORs were adjusted by age and sex. Model 2: ORs were adjusted by age, sex, and BMI. Model 3: ORs were adjusted by age, sex, BMI, and SBP. Model 4: ORs were adjusted by age, sex, BMI, SBP, parental history of hypertension, smoking habit (never, former, current), log-triglycerides, log-γ-glutamyltransferase, and uric acid.

Table 3. Odds ratio (95% CI) for the development of hypertension at 5 years after baseline according to quartiles of fasting plasma glucose (FPG) or HbA1c concentrations

	Quartiles (Q) of FPG				P-*trend*
	Q1 (< 4.9 mmol l^{-1}, < 89 mg dl^{-1})	*Q2 (4.9– < 5.2 mmol l^{-1}, 89–93 mg dl^{-1})*	*Q3 (5.2– < 5.6 mmol l^{-1}, 94–99 mg dl^{-1})*	*Q4 (⩾ 5.6 mmol l^{-1}, ⩾ 100 mg dl^{-1})*	
Incident cases/N	166/2322	263/2493	288/2500	381/2269	
Unadjusted model	1.00 (Reference)	1.53 (1.25, 1.88)	1.69 (1.38, 2.07)	2.62 (2.16, 3.18)	< 0.001
Adjusted model 1, age and sex	1.00 (Reference)	1.50 (1.22, 1.84)	1.62 (1.32, 1.98)	2.39 (1.95, 2.92)	< 0.001
Adjusted model 2, age, sex and BMI	1.00 (Reference)	1.35 (1.10, 1.66)	1.39 (1.13, 1.71)	1.85 (1.51, 2.28)	< 0.001
Adjusted model 3, age, sex, BMI and SBP	1.00 (Reference)	1.21 (0.98, 1.50)	1.23 (0.99, 1.53)	1.46 (1.18, 1.80)	< 0.001
Adjusted model 4, multivariate	1.00 (Reference)	1.20 (0.97, 1.49)	1.19 (0.96, 1.48)	1.37 (1.10, 1.70)	0.008
	Quartiles (Q) of HbA1c				
	Q1 (< 5.0%)	*Q2 (5.0–5.1%)*	*Q3 (5.2–5.4%)*	*Q4 (⩾ 5.5%)*	
Incident cases/N	1.00 (Reference)	213/2140	257/2272	415/2951	
Unadjusted model	1.00 (Reference)	1.04 (0.85, 1.27)	1.20 (0.99, 1.46)	1.54 (1.29, 1.84)	< 0.001
Adjusted model 1, age and sex	1.00 (Reference)	0.98 (0.80, 1.20)	1.09 (0.89, 1.32)	1.25 (1.04, 1.49)	0.006
Adjusted model 2, age, sex and BMI	1.00 (Reference)	0.92 (0.75, 1.13)	1.01 (0.83, 1.23)	1.06 (0.88, 1.28)	0.305
Adjusted model 3, age, sex, BMI and SBP	1.00 (Reference)	0.96 (0.78, 1.19)	1.05 (0.86, 1.29)	1.17 (0.97, 1.42)	0.051
Adjusted model 4, multivariate	1.00 (Reference)	0.97 (0.79, 1.20)	1.05 (0.86, 1.29)	1.15 (0.95, 1.40)	0.085

Abbreviaions: BMI, body mass index; CI, confidence interval; HbA1c, hemoglobin A1c; SBP, systolic blood pressure. Model 1: ORs were adjusted by age and sex. Model 2: ORs were adjusted by age, sex, and BMI. Model 3: ORs were adjusted by age, sex, BMI, and SBP. Model 4: ORs were adjusted by age, sex, BMI, SBP, parental history of hypertension, smoking habit (never, former, current), log-triglycerides, log-γ-glutamyltransferase, and uric acid.

attenuated after an adjustment for SBP in model 3. Results for models 3 and 4 showed that the highest quartile category of FPG (Q4) was predictive of hypertension. On the other hand, compared with the lowest quartile of HbA1c (Q1: < 5.0%), only the highest quartile category (Q4: HbA1c ⩾ 5.5%) was predictive of hypertension in the unadjusted model and model 1; the Q4 category of HbA1c was not predictive of the development of hypertension after adjustment for BMI in model 2 or if other variables were included in the model (models 3 and 4). Results for all models showed that the ORs for the development of hypertension among high normal HbA1c concentrations (Q2 and Q3) were not significantly elevated.

Figure 1 shows results of crude ORs according to a combination of glycemic markers and age, BMI or a prehypertensive state. We observed that individuals with an overlap between elevated FPG (⩾ Q3 categories with FPG ⩾ 5.2 mmol l^{-1}) and being older (panel a), overweight or obese (panel b) or having prehypertension (panel c) were at a substantially elevated risk for hypertension compared with those without two of those three factors. Similar results were observed for HbA1c and these factors (panels d–f).

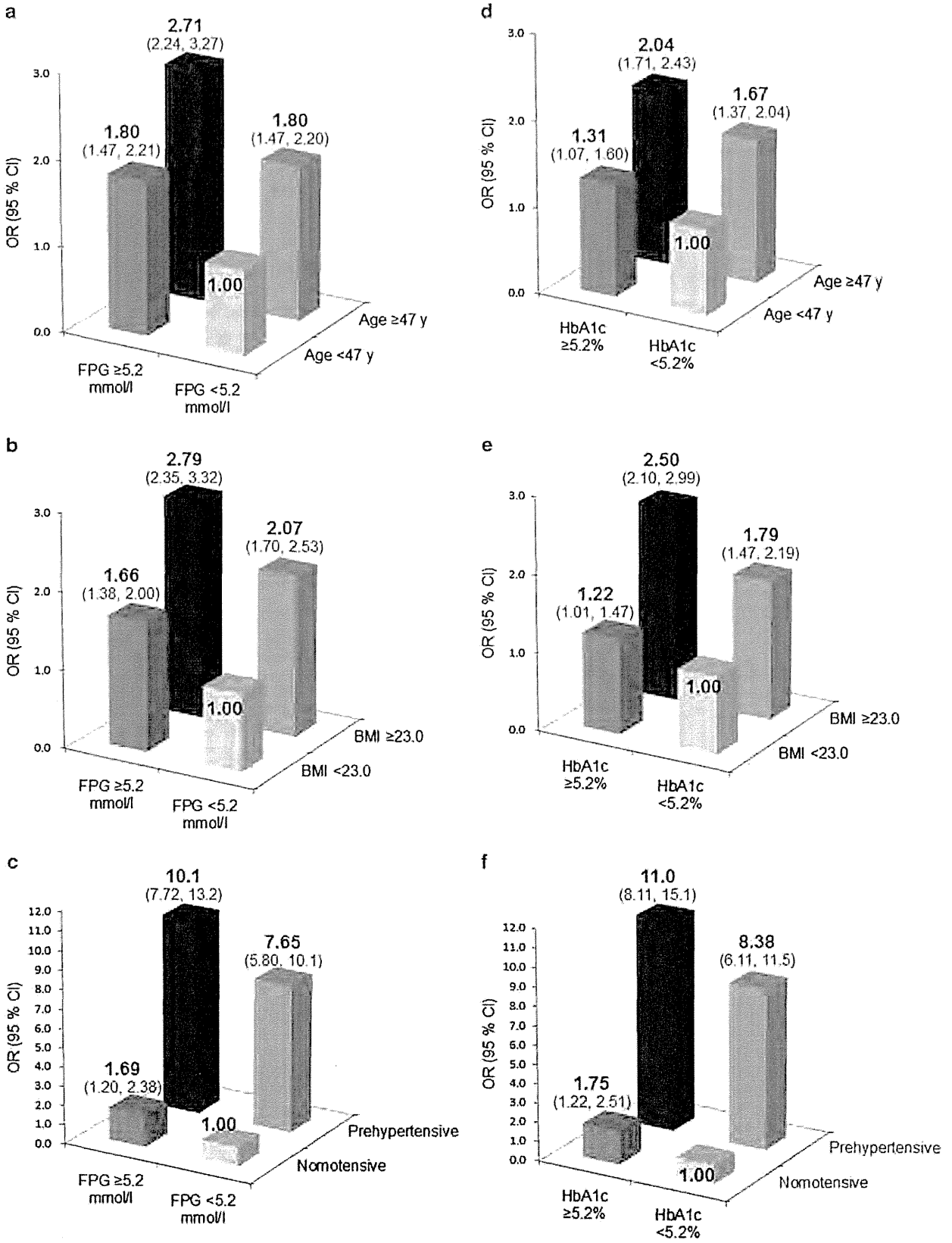

Figure 1. Crude OR (95% CI) by a combination of age, BMI, hypertensive state and glycemic markers for the development of hypertension 5 years after the baseline examination. Participants were categorized by groups according to median FPG (**a**–**c**) or HbA1c (**d**–**f**) values.

DISCUSSION

In this study of apparently healthy Japanese individuals without known diabetes and hypertension, there was a significant positive association between fasting glucose or HbA1c concentrations and the risk of developing hypertension. The role of glucose concentrations in this association was more obvious than that of HbA1c after BMI at the baseline examination was included in the multivariate-adjusted model. Our results showed that individuals with an overlap between elevated fasting glucose or HbA1c concentrations and being older, overweight/obese or prehypertensive, which are conventional risk factors for the development of hypertension, were at a substantially elevated risk for hypertension, which underscores the importance of considering the degree of glycemic levels along with other risk factors for the development of hypertension.

It has not been fully clarified which of the two glycemic indicators, FPG or HbA1c, at normal concentrations would be predictive of an increased risk of hypertension independently of other clinical markers. Our results regarding the degree of associations across quartiles of FPG concentrations and the increased risk of developing hypertension are in line with results among participants of the community-based Multi-Ethnic Study of Atherosclerosis,[9] although factors considered in their multivariable analysis were different from ours. The presence of impaired fasting glucose concentrations in prediabetic ranges was predictive of future hypertension independently of other metabolic factors in a recently reported study of Japanese adults.[12] We observed that the effect of elevated FPG concentrations on the development of hypertension was slightly attenuated after adding SBP and various non-laboratory and metabolic risk factors for hypertension[15–17,19,20] in the same model. Pathophysiological mechanisms for the association of diabetes with hypertension would be influenced by many factors, including insulin resistance; the adjustment for factors associated with insulin resistance, such as γ-glutamyltransferase, triglycerides or uric acid, might attenuate the association. Nonetheless, our findings underscore the importance of normoglycemic ranges of FPG concentrations, which could contribute to detecting individuals at high risk of developing hypertension independently of BMI.

Elevated prediabetic ranges of HbA1c concentrations among individuals not previously diagnosed with diabetes were reported to be predictive of the development of hypertension (hypertension indicated by a self-reported history of medication use or diagnosis of hypertension) independently of BMI, waist-to-hip ratio and other factors in a cohort of the Atherosclerosis Risk in Communities Study (ARIC); an additional analysis that investigated the role of FPG concentrations suggested that results for FPG were similarly predictive although slightly weaker than those for HbA1c.[11] On the other hand, results of studies from the ARIC using the definition of hypertension indicated by high blood pressure measurements or medication use showed that the association of HbA1c concentrations and risk of hypertension was attenuated after inclusion of BMI and waist-to-hip ratio in a multivariate-adjusted model.[11] The Women's Health Study showed that an elevated HbA1c within normal ranges of HbA1c $< 6.5\%$ were associated with an increased risk of hypertension, but this association was not significant after adjustment for BMI in a multivariate-adjusted model.[10] In this cohort of Japanese individuals, we also observed that HbA1c was not predictive of hypertension particularly after we considered BMI at the baseline examination; an overweight state rather than elevated HbA1c concentrations had more influence on the elevated odds ratio for the development of hypertension. However, FPG was still significantly predictive of hypertension in the multivariate-adjusted model. Other studies reported that higher postprandial glucose concentrations at 2 h during an oral glucose tolerance test were predictive of future hypertension after adjustment for FPG and other clinical variables, but no significant association was observed between FPG and hypertension in the same model.[22,23] Although FPG concentrations reflect the glycemic state at one point in time, HbA1c values can be influenced by other glycemic states, including postprandial glucose concentrations. We cannot determine the mechanisms for our findings from this observational study. Based on results from several epidemiological studies, hyperinsulinemia and the insulin sensitivity index were predictive of hypertension.[2,22,24,25] As elevations of HbA1c are influenced by the glycation of proteins in the body, which is secondary to high glucose concentrations,[26] glucose concentrations compared with those of HbA1c might more directly reflect the pathogenesis of the development of hypertension based on hyperinsulinemia and insulin resistance. Additionally, many studies showed that discordance would exist between prediabetic or diabetic ranges of glucose and HbA1c tests.[27–31] This might have influenced our observations that only the highest quartile category of HbA1c (HbA1c $\geqslant 5.5\%$) was predictive of the incidence of hypertension.

Another possible issue would be aging. In a cross-sectional analysis of non-diabetic individuals from the EPIC-Potsdam cohort study, a significant positive association of HbA1c concentrations with arterial hypertension was completely removed after adjustment for age and BMI.[32] HbA1c concentrations were positively associated with age in non-diabetic individuals even after exclusion of subjects with impaired fasting glucose and/or impaired glucose tolerance;[33] being older also increased the risk of developing hypertension.[15–17] Therefore, the role of HbA1c in predicting hypertension was attenuated after adjustment for age in our study; however, HbA1c could be predictive of the incidence of hypertension, particularly among younger people.

A cross-sectional analysis indicated a high prevalence of the coexistence of prehypertensive and prediabetic states in seemingly healthy US adults.[34] We showed that the presence of hyperglycemia along with prehypertension, older age or overweight further increased the risk of hypertension, suggesting the importance of assessing the risk of future hypertension by also considering the glycemic status. There has been an attempt to consider multiple risk factors in predicting the development of hypertension.[17,35] How the inclusion of glycemic markers in addition to other predictors of hypertension would improve risk prediction and discriminatory ability should be further investigated in detail.

Strengths of our study include the relatively large number of participants and the fact that an important topic was examined that could contribute to identifying individuals who need further detailed assessments. Several limitations should be considered. We did not have data on visceral adiposity or waist circumference, serum insulin and postprandial glucose concentrations for all of the study participants and could not investigate the association under study in detail by including these factors. Blood pressure data were based on results of measurements at a single visit, and these measurements can vary according to various external factors; therefore, whether these measurements reflected the actual blood pressure levels in each participant is unknown. Our study participants consisted of individuals who had a routine health examination. These participants might pay more attention to health behaviors than those who do not undergo such examinations. Further investigations are needed to confirm our findings in other study populations.

In conclusion, higher glucose concentrations within normoglycemic ranges, but not HbA1c within a normal range, were associated with an increased risk of developing hypertension among apparently healthy Japanese individuals. Elevated glycemic markers should be checked, particularly among individuals with conventional risk factors for hypertension, such as overweight, older age or prehypertension.

What is known about the topic

- Although elevated glycemic markers of glucose and HbA1c concentrations have been associated with the development of hypertension, whether this association could be observed below prediabetic ranges has not been determined.

What this study adds

- Higher glucose concentrations within normoglycemic ranges rather than higher, although normal, HbA1c levels were more greatly associated with an increased risk of the development of hypertension.
- Our findings underscore the point that individuals with an overlap between elevated fasting glucose or HbA1c concentrations and being older, overweight or prehypertensive, which are conventional risk factors for hypertension, were at substantially elevated risk for hypertension.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Metabolically Healthy Obesity, Presence or Absence of Fatty Liver, and Risk of Type 2 Diabetes in Japanese Individuals: Toranomon Hospital Health Management Center Study 20 (TOPICS 20)

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Objective: We investigated whether the metabolically healthy obese (MHO) phenotype was associated with an increased risk of the development of diabetes. If so, we aimed to determine what factors could explain this finding.

Design, Setting, and Participants: Studied were 8090 Japanese individuals without diabetes. Metabolic health status was assessed by common clinical markers: blood pressure, triglycerides, high-density lipoprotein-cholesterol, and fasting glucose concentrations. The cutoff value for obesity or normal weight (NW) was a body mass index of 25.0 kg/m^2.

Results: The 5-year incidence rate of diabetes was 1.2% (n = 58 of 4749) in metabolically healthy NW (MHNW) individuals, 2.8% (n = 20 of 719) in MHO individuals, 6.0% (n = 102 of 1709) in metabolically abnormal NW individuals, and 10.3% (n = 94 of 913) in metabolically abnormal obese individuals. Although MHO individuals had no or one metabolic factor, 47.8% had ultrasonographic fatty liver (FL). The MHO group had a significantly increased risk of diabetes compared with the MHNW group [multivariate adjusted odds ratio (OR) 2.23 (95% confidence interval [CI] 1.33, 3.75)], but this risk was attenuated after adjustment for FL. Compared with the MHNW/non-FL group, the risk of diabetes in the MHO/non-FL group was not significantly elevated [OR 1.01 (95% CI 0.35, 2.88)]. However, the MHO/FL and MHNW/FL groups had similarly elevated risks of diabetes [OR 4.09 (95% CI 2.20, 7.60) and 3.16 (1.78, 5.62), respectively].

Conclusions: Almost half of the MHO participants had FL, which partially explained the increased risk of diabetes among the obese phenotypes. The presence of FL should be evaluated to assess whether an individual was actually in a metabolically benign state for the prediction of diabetes. (*J Clin Endocrinol Metab* 99: 2952–2960, 2014)

Overweight, obesity, and the presence of metabolic abnormalities increase the risk of development of type 2 diabetes (1, 2). The concept of metabolically healthy obesity or benign obesity, that is, obesity not associated with obesity-related metabolic abnormalities, is not new (3–5). Different phenotypes of obesity were associated

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Abbreviations: AUCROC, area under the receiver-operating characteristic curve; BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IFG, impaired fasting glucose; MANW, metabolically abnormal and normal weight; MAO, metabolically abnormal and overweight or obese; MHNW, metabolically healthy and normal weight; MHO, metabolically healthy and overweight or obese; OR, odds ratio.

with the presence of different clinical characteristics in human subjects (6–11). Consideration of different obese phenotypes has been an important clinical issue with regard to preventing and delaying the onset of type 2 diabetes (5, 12–14).

To date, several prospective cohort studies have investigated the combined effect of an elevated body mass index (BMI) and the presence of metabolic abnormalities (such as hyperglycemia, dyslipidemia, or hypertension) or insulin resistance in the development of diabetes (15–24). Results (15–24) suggest that a metabolically healthy obese phenotype might be associated with a nonsignificant or significant increased risk of the development of diabetes in comparison with metabolically healthy nonobese individuals as defined in each study. However, these studies used different definitions for metabolic health (healthy or unhealthy), and it is questionable whether the definitions of metabolic health or the categorization of obese phenotypes used in those previous studies (15–24) were adequate to predict future diabetes.

The absence of a universal definition for the metabolically healthy obese phenotype has been raised as an important issue. Lacking such a definition might result in the misclassification of some individuals who actually have a high-risk phenotype as having a low-risk phenotype. A study suggested that the clustering of overweight, insulin resistance, and fatty liver was common (20) and that liver enzymes or an accumulation of fat in liver could play important roles in differentiating obese phenotypes at high risk of future diabetes. Therefore, we aimed to investigate whether metabolically healthy obese individuals were significantly at high risk of developing type 2 diabetes compared with metabolically healthy nonobese (or nonoverweight) Japanese individuals. In addition, if the risk of developing diabetes in those with metabolically healthy obesity (defined by BMI and metabolic factors) was increased, we investigated what factors could partially explain that elevated risk.

Materials and Methods

Study participants

The Toranomon Hospital Health Management Center Study included a cohort consisting mainly of apparently healthy Japanese government employees who had annual examinations for routine health screening in addition to some participants from the general public. All participants were interviewed at each examination using standard questionnaires that gathered information on demographic characteristics, health-related habits, and medical history. A total of 29 584 individuals had a baseline health examination during the period from 1997 to 2002. Among the 29 584 individuals, we retrospectively reviewed data on 9344 individuals who had a reexamination at our center 5 years (2002–2007) after the initial examination. We excluded individuals with diabetes at the baseline examination (n = 397), those with positive test results for either hepatitis B surface antigen or hepatic C antibody (n = 345), or a self-reported history of liver cirrhosis (n = 8). Then data on 8618 individuals were available for the current analysis. After excluding individuals with missing data on self-report of lifestyle characteristics as shown in Table 1 (n = 528), this study included a total of 8090 individuals (5884 men and 2206 women) aged 24–80 years without diabetes. Diagnosis of type 2 diabetes was made according to the American Diabetes Association criteria of a fasting plasma glucose level of 7.0 mmol/L or greater, self-reported clinician-diagnosed diabetes, or glycated hemoglobin (HbA1c) of 6.5% or greater (≥48 mmol/mol) (25). The study protocol followed the Japanese Government's Ethical Guidelines Regarding Epidemiological Studies in accordance with the Declaration of Helsinki and was reviewed by the Institutional Review Board at Toranomon Hospital.

Measurements of clinical markers

A standard questionnaire was used for assessing physical activity habits (any physical activity for 20–30 min or more at least once weekly); smoking habits; current alcohol consumption; and self-reported histories of dyslipidemia, hypertension, or diabetes. We calculated the average alcohol consumption (grams of ethanol per day) by multiplying the usual quantity of alcohol consumed per occasion by the frequency of alcohol consumption. Height and weight were measured without shoes or heavy clothing, and BMI was calculated. Blood pressure was measured by trained hospital staff with the subject in a sitting position. Blood samples were collected after an overnight fast (12 h), and measurements were made using an automatic clinical chemistry analyzer (LABOSPECT 008; Hitachi). Blood glucose, serum triglycerides, total cholesterol, and high-density lipoprotein (HDL)-cholesterol concentrations were measured by enzymatic methods. HbA1c was assessed by HPLC. The value for HbA1c was estimated as the National Glycohemoglobin Standardization Program value (%) calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society) (%) × 1.02 + 0.25% (26).

The diagnosis of fatty liver was based on the presence of an ultrasonographic pattern consistent with bright liver (brightness and posterior attenuation) with stronger echoes in the hepatic parenchyma than in the renal or spleen parenchyma, vessel blurring, and narrowing of the lumen of the hepatic veins. Each ultrasonograph was performed by one of five technicians specialized in ultrasound (one ultrasonographer staffed each examination table). All ultrasonographic images obtained by the technicians were stored as photocopies. Two gastroenterologists expert in ultrasonography reviewed the photocopies and made the diagnosis of fatty liver without reference to any of the participants' data. Ultrasound tests were performed with a high-resolution, real-time scanner (model SSD-2000; Aloka Co, Ltd; Mode Logic-700 MR; GE-Yokokawa Medical Systems).

Assessment of metabolic health status

A cutoff point of BMI of 25 kg/m^2 was used to define overweight/obesity (≥ 25.0 kg/m^2) or normal weight (< 25.0 kg/m^2). We introduced cutoffs for four metabolic factors [impaired fasting glucose (IFG), hypertension, hypertriglyceridemia, low HDL-cholesterol concentration] using International Diabetes Federation definitions (27). Data on waist circumference, vis-

Table 1. Characteristics of Study Participants at the Baseline Examination

	MHNW	MHO	*P* Value[a]	MANW	MAO	*P* Value[b]
n, % of total participants	4749 (58.7)	719 (8.9)		1709 (21.1)	913 (11.3)	
Females	1680 (35.4)	156 (21.7)	<.001	267 (15.6)	103 (11.3)	.002
Parental history of diabetes, yes	615 (13.0)	107 (14.9)	.154	282 (16.5)	155 (17.0)	.755
Age, y	48.1 (8.1)	47.0 (7.6)	<.001	49.9 (8.3)	47.4 (7.4)	<.001
BMI, kg/m^2	21.5 (2.0)	26.6 (1.6)	<.001	22.6 (1.6)	27.1 (2.0)	<.001
Smoking habit			<.001			.138
Never	2672 (56.3)	352 (49.0)		753 (44.1)	374 (41.0)	
Former	935 (19.7)	176 (24.5)		444 (26.0)	232 (25.4)	
Current	1142 (24.0)	191 (26.6)		512 (30.0)	307 (33.6)	
Alcohol consumption			<.001			.377
None	969 (20.4)	105 (14.6)		263 (15.4)	125 (13.7)	
<20 g/d by women or <30 g/d by men	2609 (54.9)	433 (60.2)		879 (51.4)	492 (53.9)	
≥20 g/d by women or ≥30 g/d by men	1171 (24.7)	181 (25.2)		567 (33.2)	296 (32.4)	
Physically active, yes	2327 (49.0)	345 (48.0)	.611	816 (47.7)	439 (48.1)	.870
Hypertension[c]	1068 (22.5)	248 (34.5)	<.001	1246 (72.9)	716 (78.4)	.002
Triglycerides ≥1.7 mmol/L or treatment	308 (6.5)	86 (12.0)	<.001	990 (57.9)	602 (65.9)	<.001
HDL-cholesterol <1.03 mmol/L in males or <1.29 mmol/L in females	352 (7.4)	64 (8.9)	.160	704 (41.2)	418 (45.8)	.024
Fasting plasma glucose 5.6–6.9 mmol/L	454 (9.6)	106 (14.7)	<.001	1009 (59.0)	559 (61.2)	.277
Total number of metabolic factors			<.001			<.001
None	2567 (54.1)	215 (29.9)		0 (0)	0 (0)	
One factor	2182 (45.9)	504 (70.1)		0 (0)	0 (0)	
Two factors	0 (0)	0 (0)		1238 (72.4)	524 (57.4)	
Three factors	0 (0)	0 (0)		411 (24.0)	309 (33.8)	
Four factors	0 (0)	0 (0)		60 (3.5)	80 (8.8)	
γ-Glutamyltransferase, U/L	27 (18, 44)	45 (27, 75)	<.001	43 (27, 73)	63 (40, 102)	<.001
Alanine aminotransferase, U/L	18 (14, 24)	26 (19, 37)	<.001	23 (17, 31)	32 (23, 48)	<.001
Fatty liver, yes	536 (11.3)	344 (47.8)	<.001	544 (31.8)	650 (71.2)	<.001

Data are n (percentage), mean ± SD or median (25th, 75th).

[a] *P* values between MHNW and MHO groups. *P* values were tested by a χ^2, median test, or *t* test.

[b] *P* values between MANW and MAO groups. *P* values were tested by a χ^2 test, median test, or *t* test.

[c] Hypertension was indicated by systolic blood pressure of 130 mm Hg or greater, diastolic blood pressure of 85 mm Hg or greater, or medical treatment.

ceral fat, fasting insulin, and C-reactive protein concentrations were not available for study participants, although we acknowledge that these markers can be used to define metabolic health (12–14). Individuals with a systolic blood pressure of 130 mm Hg or greater and/or a diastolic blood pressure of 85 mm Hg or greater or who were under medical treatment were considered to have hypertension. Elevated triglycerides was indicated by 150 mg/dL (1.7 mmol/L) or greater or treatment of hyperlipidemia, and reduced HDL-cholesterol was indicated by less than 40 mg/dL (1.03 mmol/L) in men and less than 50 mg/dL (1.29 mmol/L) in women. IFG was indicated by 100–125 mg/dL (5.6–6.9 mmol/L).

In the context of obesity, a metabolically healthy state was considered if none or one of the metabolic factors based on the International Diabetes Federation definition was present, and a metabolically abnormal state was declared if two or more metabolic factors were present (27). Then participants were categorized at the baseline examination into four phenotypes: 1) metabolically healthy and normal weight (MHNW), 2) metabolically healthy and overweight or obese (MHO), 3) metabolically abnormal and normal weight (MANW), or 4) metabolically abnormal and overweight or obese (MAO). Changes in the prevalence rate of overweight or obesity, metabolic health, and fatty liver among the four phenotypes were examined 5 years after the baseline examination.

Statistical analysis

A logistic regression analysis was performed to calculate odds ratios (ORs) for the development of diabetes. To investigate the impact of factors that influenced the association between the four phenotypes and diabetes, we analyzed data using models with the following adjustments: age and sex (model 1); age, sex, parental history of diabetes, smoking habit, physical activity habit, and alcohol consumption (model 2); model 2 + IFG (model 3); model 2 + log-transformed γ-glutamyltransferase and log-transformed alanine aminotransferase (ALT) (model 4); and model 2 + fatty liver (model 5). We also performed an additional analysis when we included the IFG state into model 2 and assessed the effect of liver enzymes (model 6) or fatty liver (model 7). We also assessed the area under the receiver-operating characteristic curve (AUCROC) for future diabetes and net reclassification improvement (28) by the use of three risk categories (<5%, 5%–15%, and >15%) by adding an assessment of fatty liver into a prediction model for the development of diabetes that included the obese phenotypes (four groups), age, sex, parental history of diabetes, and IFG. An analysis was performed with IBM SPSS Statistics version 19 or STATA software version 11 (StataCorp). The statistical significance was considered for $P < .05$.

Results

Among all participants, the prevalence of MHNW, MHO, MANW, or MAO was 58.7% (n = 4749), 8.9% (n = 719), 21.1% (n = 1709), or 11.3% (n = 913), respectively. Of the overweight/obese individuals, 44.1% (n = 719 of 1632) were not classified as metabolically abnormal based on the definition used in this study (Table 1). Of metabolically healthy individuals, 13.1% (n = 719 of 5468) were overweight or obese. Compared with MHNW individuals, MHO individuals were more likely to be male and younger and have had a history of a smoking habit or a current drinking habit, have elevated values for liver enzymes, have a higher prevalence of fatty liver, or have a higher prevalence of 1 metabolic factor.

Of the total participants, 25.6% (n = 2074 of 8090) had fatty liver, and the presence of fatty liver was high at 47.8% among the MHO individuals. When we performed logistic regression analysis and calculated the age- and sex-adjusted ORs for fatty liver at the baseline examination, results showed that compared with MHNW individuals, MHO, MANW, and MAO individuals had a significantly elevated OR [95% confidence interval (CI)] of 6.70 (5.62, 7.99), 3.22 (2.80, 3.70), and 16.8 (14.1, 19.9), respectively. Results were fundamentally the same if we calculated age- and sex-adjusted ORs among the 5875 individuals who consumed less than 20 g/d of alcohol (for women) or less than 30 g/d of alcohol (for men) [MHO, OR 7.52 (95% CI 6.13, 9.22); MANW, OR 3.75 (95% CI 3.17, 4.42); and MAO, OR 20.1 (95% CI 16.2, 24.9) compared with the MHNW phenotype].

During the 5-year follow-up period (median 1824 d, range 1473–2178 d), 274 individuals developed diabetes (83 had a history of clinician diagnosed diabetes). The crude incidence rate of diabetes was 1.2% (n = 58 of 4749) in MHNW, 2.8% (n = 20 of 719) in MHO, 6.0% (n = 102 of 1709) in MANW, and 10.3% (n = 94 of 913) in MAO phenotypes. Among the MHO individuals, 85.1% remained overweight (BMI $\geq$ 25 kg/m^2) 5 years after the baseline examination, and their metabolic risk profiles had worsened during that period (Supplemental Table 1). Of the MHO group, 34.2% (n = 246 of 719) had either type 2 diabetes or two or more metabolic abnormalities at the follow-up examination. Therefore, these individuals were no longer metabolically healthy 5 years after the baseline examination. In the MHNW group, 16.5% (n = 784 of 4749) newly developed either diabetes or a metabolically abnormal state. Of the MANW group, 9.3% (n = 159 of 1709) had a BMI of 25.0 kg/m^2 or greater at the follow-up examination, whereas 34.1% (n = 582 of 1709) had not developed diabetes and had achieved a metabolically healthy state. Of the MAO individuals at the baseline examination, we observed that 26.0% (n = 237 of 913) had not developed diabetes and had achieved a metabolically healthy state (MHNW or MHO) at the follow-up examination.

Age- and sex-adjusted OR for the development of diabetes was 2.29 (95% CI 1.37, 3.84) for MHO individuals, 4.62 (95% CI 3.31, 6.44) for MANW individuals, and 8.86 (95% CI 6.29, 12.5) for MAO individuals compared with MHNW individuals (model 1 in Table 2). Adjustment for lifestyle factors and parental history of diabetes did not greatly alter the association (model 2). After we adjusted for the presence of IFG at the baseline examination (model 3), ORs were attenuated, especially for the metabolically abnormal individuals [MANW, OR 1.51 (95% CI 1.04, 2.19); MAO, OR 2.87 (95% CI 1.96, 4.20)], although these phenotypes were still associated with a significantly increased risk of diabetes.

We performed a sensitivity analysis of individuals without IFG at the baseline examination, although only a small number of incident cases of diabetes was found among these individuals (n = 56 of 5962). Results showed that the age- and sex-adjusted OR (95% CI) for the development of diabetes was 2.99 (1.42, 6.33) in MHO (cases/total, n = 10 of 613), 2.23 (1.05, 4.72) in MANW (n = 10 of 700), or 6.06 (2.96, 12.4) in MAO (n = 12 of 354) compared with MHNW individuals (n = 24/4295). Adjustment for liver enzymes in model 4 slightly attenuated the OR for diabetes in the MHO phenotype. The MHO individuals did not have a significantly increased OR independently of the presence of fatty liver in model 5 [OR 1.54 (95% CI 0.90, 2.62)], whereas the MANW and MAO individuals had a significantly increased OR of 3.59 (95% CI 2.55, 5.06) and 4.96 (3.39, 7.25), respectively, compared with the MHNW individuals. Only MAO individuals had a significantly increased risk of the development of diabetes shown by the results of model 6 [OR 1.92 (95% CI 1.28, 2.87)] or model 7 [OR 1.73 (1.15, 2.60)]. When we calculated the ORs among the individuals with an alcohol consumption of less than 20 g/d (for women) or less than 30 g/d (for men), the MHO group did not have an elevated risk of diabetes in model 7, with an adjusted OR 1.05 (95% CI 0.54, 2.06).

We then assessed the combined effect of metabolic health status and fatty liver at the baseline examination on the development of diabetes (Figure 1). The MHNW/without fatty liver group had the lowest incidence rate of diabetes (0.9%), whereas the MHO/without fatty liver group had a similarly low incidence rate of diabetes (1.1%). Among the MHO/without fatty liver group (n = 375), only four had developed diabetes. On the other hand, the MHO/fatty liver group had an elevated incidence rate (4.7%) as did the MHNW/fatty liver group (3.5%). The incidence rate of diabetes was markedly high

Table 2. ORs for the Development of Type 2 Diabetes at 5 Years After the Baseline Examination According to Metabolic Phenotypes

Model	MHNW	MHO	MANW	MAO
Total participants				
Cases/n	58/4749	20/719	102/1709	94/913
1. Age, sex	1.00 (Referent)	2.29 (1.37, 3.84)	4.62 (3.31, 6.44)	8.86 (6.29, 12.5)
2. Lifestyle factors, parental diabetes[a]	1.00 (Referent)	2.23 (1.33, 3.75)	4.41 (3.16, 6.17)	8.50 (6.02, 12.0)
3. IFG[b]	1.00 (Referent)	1.92 (1.13, 3.26)	1.51 (1.04, 2.19)	2.87 (1.96, 4.20)
4. Liver enzymes[c]	1.00 (Referent)	1.70 (1.003, 2.88)	3.82 (2.72, 5.37)	5.57 (3.85, 8.07)
5. Fatty liver[d]	1.00 (Referent)	1.54 (0.90, 2.62)	3.59 (2.55, 5.06)	4.96 (3.39, 7.25)
6. IFG, liver enzymes[e]	1.00 (Referent)	1.50 (0.87, 2.56)	1.35 (0.92, 1.96)	1.92 (1.28, 2.87)
7. IFG, fatty liver[f]	1.00 (Referent)	1.32 (0.76, 2.27)	1.28 (0.88, 1.87)	1.73 (1.15, 2.60)
Participants without excessive alcohol consumption				
Cases/n	43/3578	13/538	70/1142	73/617
1. Age, sex	1.00 (Referent)	2.02 (1.08, 3.79)	4.78 (3.22, 7.07)	10.5 (7.05, 15.6)
2. Lifestyle factors, parental diabetes[a]	1.00 (Referent)	1.97 (1.05, 3.70)	4.57 (3.08, 6.79)	10.0 (6.71, 14.9)
3. IFG[b]	1.00 (Referent)	1.74 (0.91, 3.31)	1.63 (1.05, 2.53)	3.49 (2.24, 5.46)
4. Liver enzymes[c]	1.00 (Referent)	1.49 (0.79, 2.84)	4.06 (2.72, 6.06)	6.52 (4.22, 10.1)
5. Fatty liver[d]	1.00 (Referent)	1.22 (0.64, 2.35)	3.45 (2.29, 5.18)	5.19 (3.33, 8.08)
6. IFG, liver enzymes[e]	1.00 (Referent)	1.38 (0.71, 2.65)	1.47 (0.94, 2.29)	2.32 (1.44, 3.74)
7. IFG, fatty liver[f]	1.00 (Referent)	1.05 (0.54, 2.06)	1.26 (0.80, 1.98)	1.81 (1.11, 2.94)

Alcohol consumption was indicated by three groups (none, alcohol < 20 g by women or < 30 g by men, and alcohol ≥ 20 g by women or ≥ 30 g by men) among total participants or two groups (none or alcohol < 20 g by women or < 30 g by men) among participants without excessive alcohol consumption.

[a] Model 2: age, sex, parental history of diabetes, smoking habit (never, former, current), physical activity habit (yes), and alcohol consumption.

[b] Model 3: model 2 + IFG (fasting glucose 5.6–6.9 mmol/L).

[c] Model 4: model 2 + log-transformed γ-glutamyltransferase and log-transformed alanine aminotransferase.

[d] Model 5: model 2 + fatty liver.

[e] Model 6: model 3 + log transformed γ-glutamyltransferase and log-transformed alanine aminotransferase.

[f] Model 7: model 3 + fatty liver.

at 8.5% in the MANW/fatty liver group and 12.6% in the MAO/fatty liver group.

Compared with the lowest risk group (MHNW/without fatty liver group), the MHO/without fatty liver group had an adjusted OR of 1.01 (95% CI 0.35, 2.88) in multivariate-adjusted model 2 (Table 3). Conversely, the MHO/fatty liver group had an OR of 4.09 (95% CI 2.20, 7.60) for future diabetes. The OR in the MAO/fatty liver group was attenuated after adjustment for IFG in the multivariate-adjusted model 2, although the OR was the highest across the eight groups. If we compared the risk of diabetes among individuals with fatty liver, the MHO/fatty liver group did not have a significantly increased risk of future diabetes compared with the MHNW/fatty liver group (Supplemental Table 2).

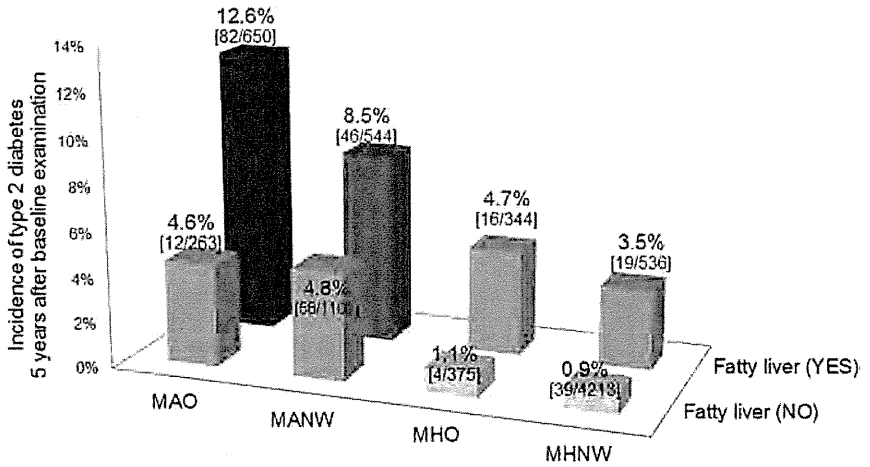

Figure 1. Combined effect of the presence of fatty liver and obese phenotypes on the incidence rate of type 2 diabetes at 5 years after the baseline examination. Data were percentages (cases/total n for each group). A cutoff point of a BMI of 25 kg/m^2 was used to define overweight/obesity (≥ 25.0 kg/m^2) or normal weight (< 25.0 kg/m^2). Metabolic health was assessed by four factors (impaired fasting glucose, hypertension, hypertriglyceridemia, and low HDL-cholesterol concentration) using the International Diabetes Federation definitions. A metabolically healthy state was considered if none or one of the metabolic factors was present and a metabolically abnormal state was declared if two or more metabolic factors were present.

A prediction model with age, sex, parental history of diabetes, IFG, and obese phenotypes had an AUCROC of 0.836 (95% CI 0.814, 0.857) for the development of diabetes. The AUCROC was slightly but a significantly ($P < .001$) improved when we added the assessment of fatty liver into the model, with an AUCROC of 0.850 (95% CI 0.829,

Table 3. ORs for the Development of Type 2 Diabetes According to the Combination of Fatty Liver and Obese Phenotypes

	MHNW	MHO	MANW	MAO
Age- and sex-adjusted model				
Fatty liver (no)	1.00 (Referent)	1.17 (0.42, 3.30)	4.92 (3.23, 7.49)	4.86 (2.51, 9.44)
Fatty liver (yes)	3.86 (2.20, 6.76)	5.31 (2.92, 9.66)	9.30 (5.94, 14.5)	15.6 (10.4, 23.4)
Multivariate-adjusted model 1[a]				
Fatty liver (no)	1.00 (Referent)	1.14 (0.40, 3.21)	4.69 (3.07, 7.16)	4.68 (2.41, 9.11)
Fatty liver (yes)	3.76 (2.14, 6.61)	5.18 (2.84, 9.47)	8.82 (5.62, 13.8)	15.0 (9.97, 22.5)
Multivariate-adjusted model 2[b]				
Fatty liver (no)	1.00 (Referent)	1.01 (0.35, 2.88)	1.54 (0.98, 2.43)	1.49 (0.74, 2.97)
Fatty liver (yes)	3.16 (1.78, 5.62)	4.09 (2.20, 7.60)	3.11 (1.92, 5.03)	5.03 (3.24, 7.80)

[a] Multivariate-adjusted model 1 included age, sex, parental history of diabetes, smoking habit (never, former, current), physical activity habit (yes), and alcohol consumption (none, alcohol < 20 g by women or < 30 g by men, and alcohol ≥ 20 g by women or ≥ 30 g by men).

[b] Multivariate-adjusted model 2 included age, sex, parental history of diabetes, smoking habit, physical activity habit, alcohol consumption, and impaired fasting glucose (fasting glucose 5.6–6.9 mmol/L).

0.871). The net reclassification improvement was 13.6% (95% CI 7.5%, 19.7%) by introducing the assessment of fatty liver in the prediction model.

Discussion

In this study of Japanese individuals, the MHO phenotype, defined by a BMI of 25 kg/m^2 or greater with no or one metabolic factor (hypertension, dyslipidemia, or IFG), was associated with a significantly higher risk of type 2 diabetes than the MHNW phenotype. At baseline, about half of the MHO individuals had ultrasonographic evidence of fatty liver, which is an established risk factor for diabetes (29, 30). The definition of metabolically healthy in this study did not differentiate according to the absence of liver fat. On the other hand, the MHO group without fatty liver had a low incidence of diabetes, and the OR was not significantly different from that for the MHNW group without fatty liver. Our findings suggest that adding information on the presence of fatty liver determined by ultrasonographic measurement into the assessment of MHNW, MHO, MHNW, and MAO phenotypes would provide clinicians and health care professionals with more precise information for predicting the risk of developing diabetes.

Studies of obese individuals suggested that the MHO group had a more favorable distribution of low visceral fat, although the total fat mass was similar between MHO and MAO (4, 8). Although we had no data on visceral fat in this study, results of a previous study indicated that ectopic fat in the liver might be more important than visceral fat in the determination of metabolically benign obesity (7). That report also showed that an obese-insulin sensitive group had less fat accumulation in the liver than a similar obese-insulin resistance group (7). A study of monozygotic twins showed that whether there was an accumulation of fat in liver influenced the presence of metabolic disturbances in obese individuals (10). A cross-sectional study of Koreans reported that MHO individuals had a high probability of fatty liver but not of preclinical atherosclerosis as assessed by the coronary artery calcification score (11). We could not determine why MHO individuals were more likely to have fatty liver at the baseline examination, and we observed that results were not influenced by excessive alcohol intake.

It was reported that fat accumulation in the liver induced hyperglycemia, dyslipidemia, subclinical inflammation, and the secretion of substances called hepatokines (such as fetuin-A) that would induce insulin resistance (31). However, a review showed that among individuals with fatty liver, 37% did not have metabolic syndrome, prediabetes, or diabetes (32). The present results showed that even in MHNW and MHO individuals, the incidence rate of diabetes was increased in the presence of fatty liver. A prospective study that investigated clustering of insulin resistance, overweight/obesity, and fatty liver showed that the clustering of these markers markedly increased the odds of developing diabetes (20). Our study introduced four metabolic factors commonly available in clinical settings to define whether an individual was metabolically healthy or unhealthy rather than using the degree of insulin resistance. Using routinely available metabolic parameters, we showed that MAO individuals who also had ultrasonographic fatty liver had a markedly elevated risk of future diabetes. Our findings may contribute to identifying patients with metabolically malignant fatty liver (32) that may substantially increase the risk of future diabetes.

Although several studies provided longitudinal data on the risk of developing diabetes in the four obese phenotypes that we examined, it is difficult to directly compare our results with those of other studies because the defini-