Fasting insulin concentrations and incidence of hypertension, stroke, and coronary heart disease: a meta-analysis of prospective cohort studies[1–3]

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ABSTRACT

Background: Insulin resistance is a precursor of numerous chronic diseases, including cardiovascular disease (CVD). The fasting insulin concentration is considered a reasonable surrogate of insulin resistance, especially among nondiabetic individuals.

Objective: We aimed to quantitatively summarize the literature on the association of fasting insulin concentrations with risk of hypertension, stroke, and coronary heart disease (CHD) by conducting a meta-analysis of prospective cohort studies.

Design: Eligible studies were identified by searching PubMed and EMBASE through January 2013. Additional information was retrieved through Google Scholar or a hand review of the reference lists from relevant articles. Prospective cohort studies that reported RRs and corresponding 95% CIs for the association of interest were identified. Data were extracted independently by 2 investigators, and the weighted RRs and 95% CIs for the associations were obtained by using a random-effects model.

Results: Of the 22 identified studies, 10 reported results on hypertension (36,617 individuals and 4491 cases), 7 on stroke (27,887 individuals and 1550 cases), and 9 on CHD (22,379 individuals and 1986 cases). Comparison of the highest with the lowest quantile of fasting insulin concentrations showed a pooled RR (95% CI) of 1.63 (1.35, 1.97) for hypertension, 1.18 (0.87, 1.60) for stroke, and 1.50 (1.28, 1.77) for CHD. Each 50-pmol/L increment in fasting insulin was associated with a 25% increase in risk of hypertension [RR: 1.25 (1.14, 1.36)] and a 16% increase in risk of CHD [RR: 1.16 (1.10, 1.22)] but was not associated with risk of stroke [RR: 0.999 (0.99, 1.01)].

Conclusions: A higher fasting insulin concentration or hyperinsulinemia was significantly associated with an increased risk of hypertension and CHD but not stroke. This meta-analysis suggests that early fasting insulin ascertainment in the general population may help clinicians identify those who are potentially at high risk of CVD. *Am J Clin Nutr* 2013;98:1543–54.

INTRODUCTION

Insulin resistance is either a precursor or a pivotal component of numerous chronic diseases (1–5) including cardiovascular disease (CVD)[4] (4), which is the leading cause of morbidity and mortality and is responsible for >70% of total mortality among patients with type 2 diabetes (6). Hyperinsulinemia, as a surrogate or a compensatory reaction of insulin resistance, may play an important role in the pathogenesis of CVD. It has been hypothesized that hyperinsulinemia precedes type 2 diabetes, which is a major risk factor for developing macrovascular complications and then becomes associated with an adverse CVD risk profile, including hypertension (6). However, whether hyperinsulinemia per se is an independent risk factor for CVD remains controversial.

Although cross-sectional and longitudinal studies have explored whether an elevated insulin concentration or insulin resistance is associated with increased CVD risk (7–12), the literature is inconsistent regarding perspective relations of fasting insulin concentrations with subsequent risk of hypertension, stroke, and coronary heart disease (CHD). Many prospective cohort studies have thus far shown that fasting insulin concentrations may predict risk of hypertension (13–20), stroke (21), and CHD (21–23) independent of other known CVD risk factors, whereas others have not [hypertension (24, 25), stroke (22, 26–30), and CHD (28, 29, 31–34)]. Therefore, in this study, we aimed to quantitatively summarize the literature on the associations between fasting insulin concentrations and risk of hypertension, stroke, and CHD by conducting a meta-analysis of prospective cohort studies.

MATERIALS AND METHODS

Search strategy

The meta-analysis was performed based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (35). First, we conducted a systematic search of published studies in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) through January 2013 using the terms "insulin or hyperinsulinemia" and

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[4] Abbreviations used: BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease.

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"hypertension or blood pressure or stroke or cerebrovascular accident or myocardial infarction or coronary heart disease" and "epidemiological studies" and "cohort/ prospective/follow-up/ longitudinal studies" and "survival analysis or proportional hazard model or Cox or hazards ratio or risk." Next, we reviewed EMBASE (http://www.elsevier.com/online-tools/embase), Google Scholar (http://scholar.google.com/), and the reference lists of the retrieved articles to identify any studies that were not identified from the preliminary literature searches. Third, to get additional data or de novo results for this meta-analysis, we contacted the authors of primary studies (19, 32).

Selection criteria

Studies were included in the meta-analysis if they met the following criteria: published in the English language, had a prospective cohort design, involved a general population, exposure was fasting insulin or hyperinsulinemia, and had an RR with 95% CI or these data could be derived from reported results.

Data extraction

Two investigators (PX and KH) assessed the eligibility of the literature independently, and any disagreements were resolved by consensus. From each retrieved article, we extracted the following data: specific outcome, name of the first author, year of publication, study name, country where the study was conducted, proportion of male sex, age at baseline, follow-up time, total number of individuals/person-years of follow-up, number of cases, exposure classification, outcome assessment, covariates that were adjusted in the analysis, and the RRs estimates with corresponding 95% CIs for corresponding categories and/or for continuous exposure.

RRs and 95% CIs transformed to their natural logarithms (ln) were used to compute the corresponding SEs. In studies in which RRs and 95% CIs were reported as per unit or per SD (either in pmol/L or μU/mL) increment in fasting insulin concentration, they were converted to a per 50-pmol/L increment consistently. If a study did not provide the linear association of fasting insulin with the outcome of interest, we estimated it by using Greenland and Longnecker's method if there were $\geq$3 categories for insulin concentrations (36), or we just calculated it under a linear assumption if there were only 2 categories. If the highest group of fasting insulin concentrations was an open range (eg, >73.27 pmol/L), then its upper limit was estimated by assuming its range as wide as the previous one.

In addition, in one study where only stratified RRs (95% CIs) for incident hypertension by status of family history of hypertension were reported (25), we pooled them with a random-effects model to get an overall estimate. Moreover, in another study in which the main effects of hyperinsulinemia (yes or no) and alcohol intake (yes or no) and their interaction on incidence of hypertension were reported, we recalculated the stratified results by alcohol status and pooled them with a random-effects model to get an overall estimate (24). Furthermore, in 2 other studies (19, 32), we contacted the authors and obtained de novo results for the meta-analysis.

Statistical analysis

We pooled RR estimates separately for each outcome using a random-effects model. We evaluated the statistical heterogeneity of the RRs by calculating the I^2 statistic; low, moderate, and high degrees of heterogeneity corresponded to I^2 values of 25%, 50%, and 75%, respectively. Publication bias was generally assessed by using Egger's (when the numbers of studies pooled was $\geq$3) or Begg's (when the numbers of studies pooled was <3) asymmetry test. If publication bias did exist, the Duval and Tweedie nonparametric "trim and fill" method was used to get the overall estimate (37). The meta-regression model was used to detect any potential modifiers.

The average of follow-up years was calculated as the sum of person-years divided by the total numbers of individuals. If unavailable, person-years were estimated by multiplying the number of individuals and the average (mean or median) of follow-up time. In stratified analyses, we examined subtypes of stroke (ischemic and hemorrhagic) and duration of follow-up ($\geq$ compared with < the median). We also stratified the data by study region, if possible. Sensitivity analyses evaluated the effect of removing a single study from the analysis, and, if using a fixed-effects model, will substantially affect the results. All analyses were performed by using STATA statistical software (version 11.0; STATA Corporation LP).

RESULTS

Literature search

As shown in **Figure 1**, we retrieved 349 related articles from PubMed. Of these, 334 articles were excluded for one of the following reasons: *1*) a review/meta-analysis, editorial, abstract, or letter to editor; *2*) not published in English; *3*) not conducted in a general population; *4*) not relating fasting insulin to an outcome of interest; *5*) fasting insulin was neither a categorical variable nor a continuous variable in original scale; *6*) not a prospective cohort design; or *7*) no RRs with 95% CIs were reported or such information could not be calculated. In addition, we identified 7 articles from EMBASE or by hand searching Google Scholar and the reference list. Therefore, 22 identified eligible studies were included in this meta-analysis.

Study characteristics

The information extracted from the 22 included independent studies, all of which were prospective cohort studies and had participants without prior diagnosed CVD at baseline, is shown in **Table 1**. For hypertension (10 studies), the total number of individuals were 36,617 with 5491 incident cases during an average 5.7 y of follow-up. For stroke (7 studies), the total number of individuals was 27,887 with 1550 incidence cases during an average of 12.3 y of follow-up. For CHD (9 studies), the total number of individuals was 22,379, with 1986 incidence cases during an average of 13.8 y of follow-up. The potential confounders included in the multivariable-adjusted model are listed in Table 1.

Fasting insulin concentrations and risk of hypertension

The result from the random-effects meta-analysis of the relation between fasting insulin concentrations and incidence of hypertension are shown in **Figure 2**. Eight studies reported RRs (95% CIs) for the highest compared with the lowest quantile. As compared with those in the lowest quantile, the pooled RR

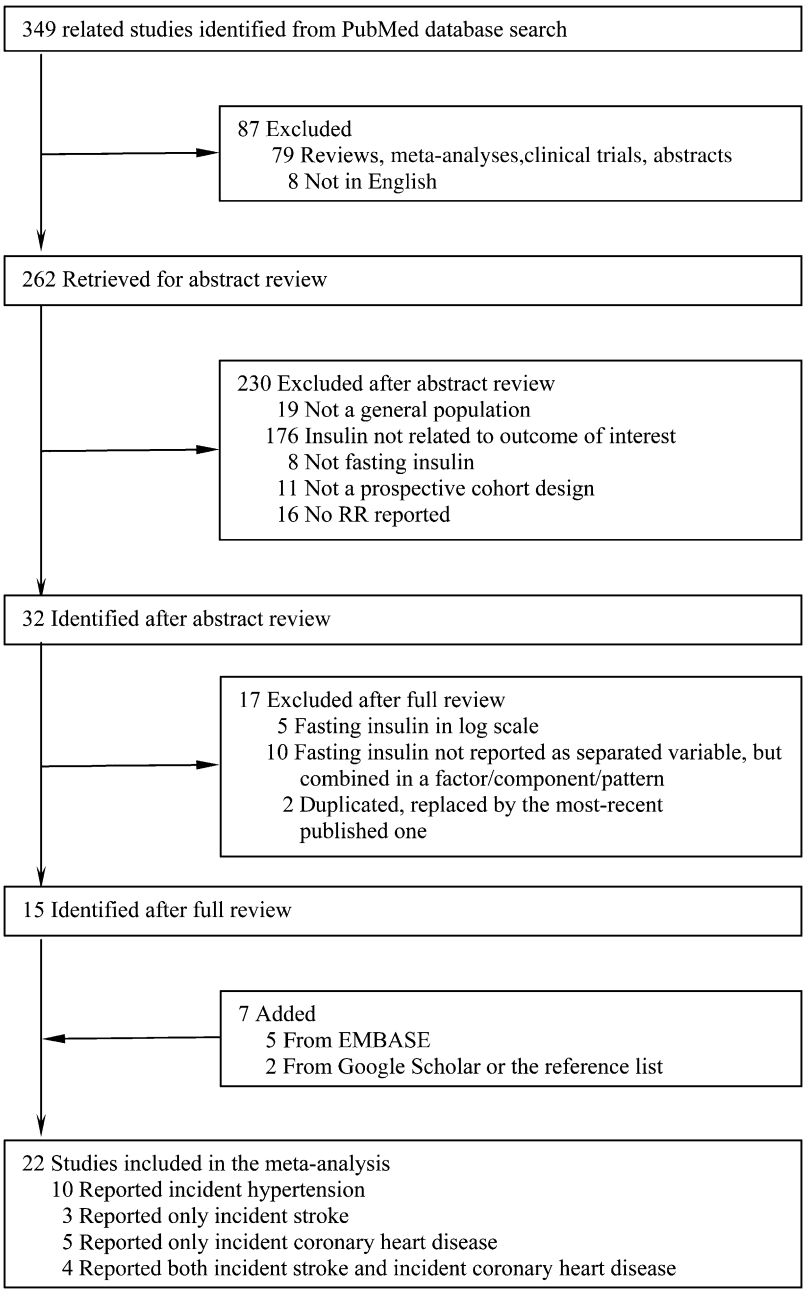

FIGURE 1. Study selection process. EMBASE, http://www.elsevier.com/online-tools/embase; Google Scholar, http://scholar.google.com/; PubMed, http://www.ncbi.nlm.nih.gov/pubmed.

for individuals in the highest quantile was 1.63 (95% CI: 1.35, 1.97) for hypertension. There was moderate heterogeneity among studies (I^2 = 59.6%, P = 0.02). No statistically significant evidence of publication bias was observed (Egger's test, P = 0.64).

The linear trend analysis involved 9 studies. The combined RR was 1.25 (1.14, 1.36) for an increment of 50 pmol/L insulin concentrations. Modest heterogeneity of effect estimates was observed (I^2 = 46.6%, P = 0.06), and Egg's test for publication bias showed no significant difference (P = 0.22). Neither study region (Eastern compared with Western countries) nor duration of follow-up modified the observed associations. Because only 2 studies reported results separately by sex, we could not assess the potential effect modification by sex.

Fasting insulin concentrations and risk of stroke

The pooled RR for the comparison of extreme quantiles of insulin concentrations was 1.18 (95% CI: 0.87, 1.60) for total stroke combining data from 6 studies. We saw high heterogeneity among studies (I^2 = 66.1%, P = 0.02), and no evidence of publication bias (Egger's test, P = 0.44) (**Figure 3**).

We found no linear trend, and the pooled RR from 6 studies was 0.999 (95% CI: 0.99, 1.01) for an increment of 50 pmol/L in insulin concentrations. There was high heterogeneity among the

TABLE 1
Characteristics of the studies included in the meta-analysis[1]

Source	Males	Age at baseline	Duration of follow-up[2]	Total no. of individuals/ person-years	No. of cases	Fasting insulin categories	Outcome assessment	Adjustment for confounders
	%	*y*	*y*					
Hypertension								
Lissner (15), 1992, Sweden	0	50 ± 0	10.7	278/2982	70	Quartiles (mU/L): ≤10, 11–13, 14–16, ≥17	SBP/DBP ≥160/95 mm Hg; current, untreated hypertension as reported by the subject to the examining physician; any type of antihypertensive therapy at the time of the visit	BMI, WHR, and weight change between the first 2 examinations
Tsuruta (16), 1996, Japan	48.9	50.0 ± 10.1	11	135/NA	62	Tertiles (pmol/L)	SBP/DBP ≥140/90 mm Hg or use of antihypertensive medication at the time of the follow-up examination	Age, sex, SBP, BMI, serum TG, serum creatinine, and alcohol consumption at baseline
Fagot-Campagna (25), 1997, The Paris Prospective Study, French	100	Median: 49.3 (43–54)[†]	3.16 ± 1.35	4149/13,118	1035	P_{90} compared with P_{10} (pmol/L) (136 compared with 29)	SBP/DBP ≥160/95 mm Hg or current use of antihypertensive medications	Age, excessive alcohol consumption, BMI, and iliac circumference by status for family history of hypertension
He (18), 1999, TOHP-1, USA	56	43.9 ± 6.2	7.1 (6.3–7.9)	377/NA	96	Continuous (pmol/L)	SBP/DBP ≥160/95 mm Hg or diagnosis by a physician	Age, sex, race, heart rate, and alcohol consumption at baseline and intervention assignment in the Trials of Hypertension Prevention, phase 1 (sodium reduction or weight loss compared with all others)
Arima (24), 2002, The Hisayma Study, Japan	35.7	56 ± 10 (40–79)	5	1133/NA	186	Tertiles (pmol/L) Men: <138, 138–234, and ≥235 Women: <180, 180–276, and ≥277	SBP/DBP ≥160/ 95 mm Hg or current use of antihypertensive medication	Age, sex, alcohol consumption, BMI, fasting glucose, TC, HDL-C, TG, parental history of hypertension, smoking habits, physical activity, and intakes of total energy, saturated fatty acids, and sodium
Cheung (17), 2008, Hong Kong CRISPS2, China	47	43.6 ± 11.2	6.4 (4–9)	1602/NA	258	Continuous (mIU/L)	SBP/DBP ≥140/90 mm Hg or a previous diagnosis of hypertension and taking antihypertensive medications	Age and sex

(Continued)

TABLE 1 (*Continued*)

Source	Males	Age at baseline	Duration of follow-up[2]	Total no. of individuals/ person-years	No. of cases	Fasting insulin categories	Outcome assessment	Adjustment for confounders
Levin (14), 2010, The MESA study, USA	49.0	59.1 ± 9.7	5	3513/14,846	965	Quartiles (pmol/L): <3.3, 3.3–4.7, 4.8–7.3, >7.3	SBP/DBP ≥140/90 mm Hg or use of an antihypertensive medication in combination with a self-report of hypertension	Age, sex, race-ethnicity, attained education, moderate/vigorous physical activity, smoking, alcohol use, BMI, and WC
Chul Sung (13), 2011, Korea	68.9	40.5 ± 5.7	5	10,894/NA	881	Quartiles (mU/L): <5.35, 5.36–6.58, 6.59–8.45, ≥8.46	SBP/DBP ≥140/90 mm Hg or history of hypertension during the follow-up period	Age, sex, smoking, alcohol use, exercise, education, SBP, DBP, fasting glucose, TG, HDL-C, uric acid, BMI, and BMI change
Xun (19), 2012, The CARDIA Study, USA	47.4	25.0 ± 3.6 (18–30)	20	3413/57,920	796	Quartiles (mU/L): <9, 9–10.9, 11.0–14.2, ≥14.3	SBP/DBP ≥140/90 mm Hg or taking antihypertensive medication at each examination	Age, sex, race, study center, BMI, physical activity, education, smoking, alcohol consumption, baseline SBP, family history of hypertension, glucose, and dietary intakes of sodium, potassium, and magnesium
Park (20), 2012, Korea	65.6	39.4 ± 6.4 (20–65)	4	11,123/NA	1142	Quartiles (pmol/L): ≤50.07, 50.14–60.42, 60.56–72.99, ≥73.27	SBP/DBP ≥140/90 mm Hg or history of hypertension during the follow-up	Age, sex, BMI, percentage weight change, smoking status, alcohol consumption, regular exercise, SBP, and fasting glucose, TG, and HDL-C concentrations at baseline
Stroke								
Pyorala (29), 1998, The Helsinki Policemen Study, Finland	100	47.4 ± 7.5 (34–64)	22	970/NA	Total: 70 Ischemic: 55 Hemorrhagic: 7	Hyperinsulinemia: $AUC_{insulin}$ quintile 5 vs. quintiles 1–4	WHO criterion (1981): a neurologic deficit observed by a physician for >24 h without other disease explaining the symptoms	Age, subscapular skinfold thickness, SBP, and smoking (yes or no)
Lakka (28), 2000, The KIHDRF Study, Finland	100	42–60	9.4 (0.3–12.8)	1521/14,297	Total: 48	Quartiles (pmol/L): <52, 52–66, 67–89, ≥90	ICD-9 codes 430–436	Age, examination year, smoking, blood leukocyte count, serum apolipoprotein B concentration, plasma fibrinogen concentration, maximal oxygen uptake

(Continued)

TABLE 1 (*Continued*)

Source	Males	Age at baseline	Duration of follow-up[2]	Total no. of individuals/ person-years	No. of cases	Fasting insulin categories	Outcome assessment	Adjustment for confounders
Lawlor (22), 2007, UK	0	60–79	Median: 4.6	3246/14,932	Total: 52	Continuous (mU/L)	Either stroke death (ICD-10 codes I60-I69, G45) or occurrence of a nonfatal stroke identified in the follow-up medical record reviews	Age, life course socioeconomic position, smoking, physical activity, BMI, WHR, HDL-C, TG, SBP, LDL-C, fasting glucose, and Hb A_{1c}
Wiberg (30), 2009, The ULSAM Study, Sweden	100	70	Median: 8.8 (0.0–11.4)	1151/9395	Total: 150	Continuous (pmol/L)	ICD-9 codes 430–436, ICD-10 codes I60-I64, G45	Hypertension, diabetes, atrial fibrillation, ECG-LVH, serum TC, and smoking
Rasmussen-Torvik (21), 2010, The ARIC Study, USA	43.2	53.8 (45–64)	18	12,323/196,498	Ischemic: 445	Quintiles (mU/L): <6, 6–8, 8 to <11, 11 to <15, ≥15	Validated definite or probable embolic or thrombotic brain infarctions	Age, sex, race, and study center
Thacker (27), 2011, The CHS Study, USA	42	73 (≥65)	12.4	3442/42,551	Ischemic: 417	Quintiles (pmol/L): 20.8–62.5, >62.5–83.3, >83.3–111.1, >111.1–722.3	Ascertained from participant report, questions at annual visits, telephone contacts every 6 mo between annual visits and after annual visits ended, and screens of hospitalizations for key ICD-9 revision codes; confirmed with information from participant interviews, medical records, test results, and brain images	Age, sex, race, estimated GFR, CHD, congestive heart failure, atrial fibrillation, peripheral arterial disease, SBP, antihypertensive medication use, triglycerides, HDL-C, and LDL-C
Wieberdink (26), 2012, Rotterdam Study, Netherlands	42.4	Median: 67.9 (≥55)	Median: 8.6	5234/42,806	Total: 366	Quintiles (pmol/L): 10–46, 47–64, 65–90, 91–430	Stroke was defined according to WHO criteria as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer or leading to death, with no apparent cause other than of vascular origin	Age, sex, and a propensity score (current smoking, SBP, BP-lowering medication use, total cholesterol, HDL-C, triglycerides, lipid-lowering medication use, von Willebrand factor, BMI, and WHR)
Coronary heart disease								
Welin (31), 1992, Sweden	100	67 ± 0	8	595/NA	66	Quintiles (mU/L): <6.3, 6.3–9.3, 9.4–12.9, 13.0–17.9, ≥18	Fatal or nonfatal MI or death from CHD	Serum TC and TG

(Continued)

TABLE 1 (*Continued*)

Source	Males	Age at baseline	Duration of follow-up[2]	Total no. of individuals/ person-years	No. of cases	Fasting insulin categories	Outcome assessment	Adjustment for confounders
Moller (23), 1995, Denmark	47.9	40 ± 0	17	1052/NA	54	Continuous (pmol/L)	ICD-8 codes 410–414	Sex, BMI, physical activity, tobacco consumption, alcohol consumption, SBP, TC, TG, and HDL-C
Pyorala (29), 1998, The Helsinki Policemen Study, Finland	100	47.4 ± 7.5 (34–64)	22	970/NA	164	Hyperinsulinemia: $AUC_{insulin}$ quintile 5 compared with quintiles 1–4	ICD-8 codes 410–413, ICD-9 codes 410–414	Age, BMI, subscapular skinfold thickness, cholesterol, triglycerides, SBP, smoking, physical activity, and AUC glucose
Lakka (28), 2000 The KIHDRF Study, Finland	100	42–60	9.3 (0.1–12.8)	1521/14,145	110	Quartiles (pmol/L): <52, 52–66, 67–89, ≥90	ICD-9 codes 410–414	Age, examination year, smoking, blood leukocyte count, serum apolipoprotein B concentration, plasma fibrinogen concentration, and maximal oxygen uptake
Yudkin (32), 2002, The Caerphilly Study, UK	100	50–64	10–14	983/NA	113	Quartiles (pmol/L): <18.4, 18.4–26.4, 26.5–39.3, ≥39.4	CHD death (ICD-9 codes 410–414), together with similarly classified hospital admissions and subjects who had developed new MI on ECG	Age and BMI
Zethelius (33), 2002, Sweden	100	50	26.7	874/NA	219	Continuous (pmol/L)	ICD-9 codes 410–414	Age at entry, BMI, SBP at office, smoking fasting glucose, serum TC, and LDL-C/HDL-C ratio
Zethelius (34), 2005, Sweden	100	70	Median: 7.9	815/5792	126	Continuous (pmol/L)	ICD-9 codes 410–414, ICD-10 codes 120–25	Serum TC, SBP, fasting plasma glucose, BMI, and smoking
Lawlor (22), 2007, UK	0	60–79	4.6	3246/14,932	174	Continuous (mU/L)	CHD death (ICD-10 codes I20-I25, I51.6) or a nonfatal myocardial infarction, angina diagnosis or coronary artery bypass, or angioplasty identified in the follow-up medical record reviews	Age, life-course socioeconomic position, smoking, physical activity, BMI, WHR, HDL-C, TG, SBP, LDL-C, fasting glucose, and Hb A_{1c}
Rasmussen-Torvik (21), 2010, The ARIC Study, USA	43.2	53.8 (45–64)	18	12,323/193,069	960	Quintiles (mU/L): <6, 6–8, 8 to <11, 11 to <15, ≥15	Definite, probable, or silent MI or definite CHD death	Age, sex, race, and study center

[1] ARIC, Atherosclerosis Risk in Communities; CARDIA, Coronary Artery Risk Development in Young Adults; CHD, coronary heart disease; CHS, Cardiovascular Health Study; DBP, diastolic blood pressure; ECG, electrocardiography; GFR, glomerular filtration rate; Hb A_{1c}, hemoglobin A_{1c}; HDL-C, HDL cholesterol; ICD, International Classification of Diseases; KIHDRF, Kuopio Ischemic Heart Disease Risk Factor; LDL-C, LDL cholesterol; LVH, left ventricular hypertrophy; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; NA, not available; TC, total cholesterol; TG, triglycerides; TOHP-1, Trials of Hypertension Prevention, phase 1; SBP, systolic blood pressure; ULSAM, Uppsala Longitudinal Study of Adult Men; WC, waist circumference; WHR, waist-hip ratio.

[2] The durations of follow-up periods were reported or calculated based on the reported person-years in the primary studies.

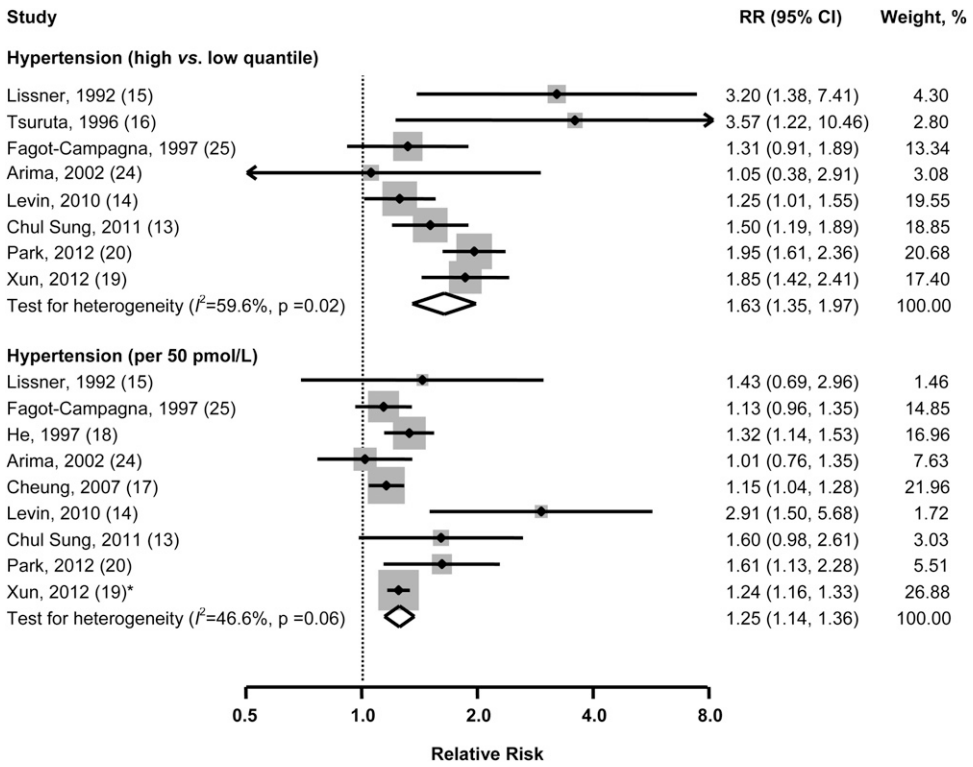

FIGURE 2. Multivariable-adjusted RRs and 95% CIs (horizontal lines) for incident hypertension. The pooled estimates (diamond data markers) were obtained by using a random-effects model. The dots indicate the adjusted RRs by comparing high with low quantiles or per 50-pmol/L increase in fasting insulin concentrations. The size of the shaded square is proportional to the percentage weight of each study. *De novo data for the meta-analysis.

studies (I^2 = 55.8%, P = 0.045). Because there was evidence of publication bias (Egger's test, P = 0.01), we used the Duval and Tweedie's nonparametric "trim and fill" method to account for the publication bias. An overall estimate of RR was 0.998 (95% CI: 0.99, 1.01).

In the stratified analysis, the pooled risk of those in the highest quantile was 1.24 (0.88, 1.76), with high heterogeneity among 3 studies (I^2 = 62.9%, P = 0.07) for ischemic stroke. We observed no evidence of publication bias (Egger's P = 0.75). Only one study reported results on hemorrhagic stroke.

On the basis of 3 studies that reported results in men, we identified a positive (RR: 1.67; 95% CI: 1.07, 2.60; high compared with low quantiles) and linear (RR: 1.20; 95% CI: 1.03, 1.40; per 50-pmol/L increment) association between fasting insulin and risk of stroke. Only one study reported results on women separately. The duration of follow-up did not substantially modify the observed associations. Because all the studies were conducted in Western countries, we could not assess the heterogeneity between eastern and Western countries. Similar results were found in the studies conducted in US and non-US countries.

Fasting insulin concentrations and risk of CHD

Ten studies were involved in the synthesis of the relation of fasting insulin concentrations with CHD (**Figure 4**). On the basis of available data from 4 studies, the pooled RR from a comparison of extreme quantiles of insulin concentrations for CHD was 1.50 (95% CI: 1.28, 1.77) with no significant heterogeneity among studies (I^2 = 0.0%, P = 0.71). No evidence of publication bias was observed (Egger's test, P = 0.28).

According to available data from 8 studies, the pooled risk of CHD per 50-pmol/L increment in insulin concentration was 1.16 (95% CI: 1.10, 1.22), with modest heterogeneity among studies (I^2 = 11.7%, P = 0.34) and no significant evidence of publication bias (Egger's test, P = 0.88).

Only one study reported results in women. On the basis of 6 studies that reported results in men, we identified a positive dose-response association (RR: 1.13; 95% CI: 1.02, 1.25; per 50-pmol/L increment). Similar results were found in the studies conducted in the United States and outside of the United States, and in studies with long-term (≥ the average time) and short-term (< the average time) follow-up periods.

Sensitivity analysis

The findings were consistent when a fixed-effects model was used (*see* Supplemental Table 1 under "Supplemental data" in the online issue). Omission of one study at a time and recalculation of the pooled RRs for the rest of the studies showed that none of the single studies substantially influenced the pooled RR for hypertension (*see* Supplemental Table 2 under "Supplemental data" in the online issue). For stroke, the pooled association changed from 1.18 (95% CI: 0.87, 1.60) to 1.29 (95% CI: 0.87, 1.91) and 1.31 (95% CI: 0.96, 1.80), respectively, when Thacker et al's study (27) and Wieberdink et al's study (26) were excluded. For CHD, the pooled estimate was attenuated from 1.50 (95% CI: 1.28, 1.77) to 1.32 (95% CI: 0.99, 1.77) with the omission of Rasmussen-Torvik et al's study (21). Omission of the other studies did not materially change the results.

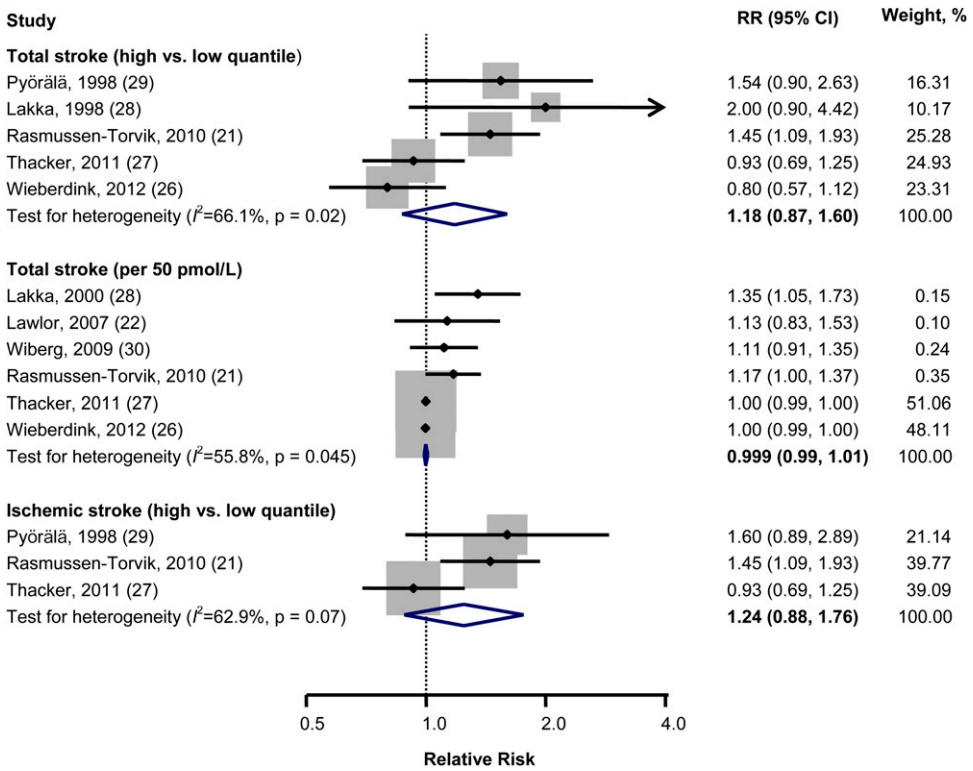

FIGURE 3. Multivariable-adjusted RRs and 95% CIs (horizontal lines) for incident stroke and its subtypes. The pooled estimates (diamond data markers) were obtained by using a random-effects model. The dots indicate the adjusted RRs by comparing high with low quantiles or per 50-pmol/L increase in fasting insulin concentrations. The size of the shaded square is proportional to the percentage weight of each study.

DISCUSSION

In this quantitative meta-analysis of prospective cohort studies, we found significant, positive, and linear associations of fasting insulin concentrations with risk of hypertension and CHD, but not stroke. The observed associations were not materially modified by follow-up period. Our ability to access the potential modifications by sex or study region was limited by a lack of information from the primary studies.

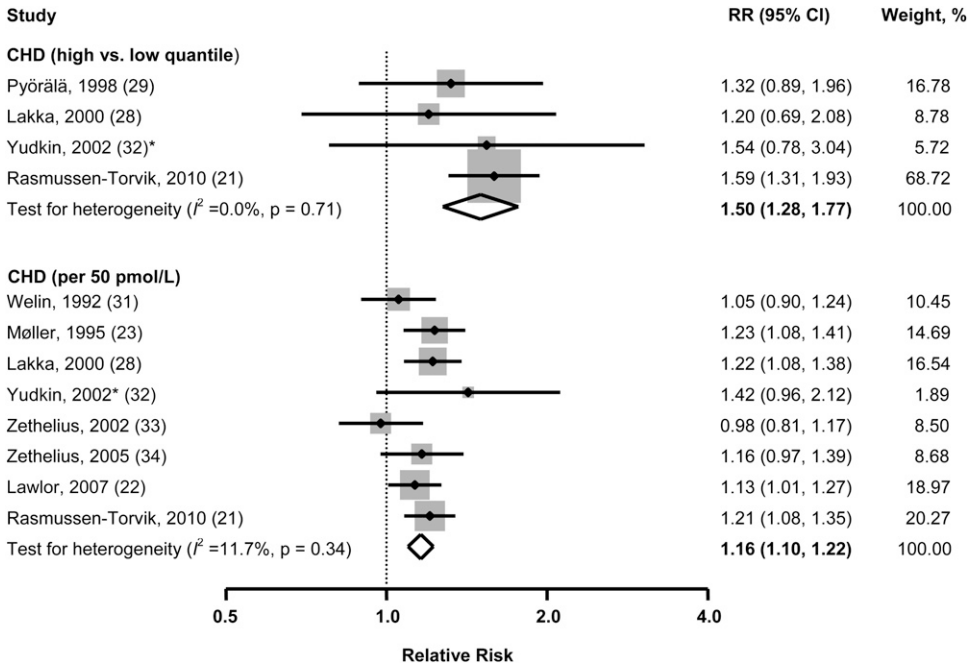

FIGURE 4. Multivariable adjusted RRs and 95% CIs (horizontal lines) for incident coronary heart disease. The pooled estimates (diamond data markers) were obtained by using a random-effects model. The dots indicate the adjusted RRs by comparing high with low quantiles or per 50-pmol/L increase in fasting insulin concentrations. The size of the shaded square is proportional to the percentage weight of each study. *De novo data for the meta-analysis. CHD, coronary heart disease.

Strengths and limitations

To date, this was the largest synthesis of prospective cohort studies to have assessed the associations of fasting insulin concentrations with incidence of hypertension, stroke, and CHD in one meta-analysis, which significantly increased the statistical power to detect potential associations. Also, our conclusions were strengthened by pooling data for estimating both dose-response relations and the RRs in a comparison of high with low concentrations of insulin. In addition, the positive association documented between fasting insulin concentration and risk of hypertension further supports the idea that elevated insulin concentrations may increase the risk of CHD through high blood pressure (BP).

Several limitations of this meta-analysis should be acknowledged. First, the inherent limitations of the primary studies may have affected our findings. For example, the possibility of residual confounding or bias due to systematic measurement errors or unmeasured factors cannot be ruled out. Second, the assay used to measure fasting insulin in a few studies (21, 28) was unspecific and had some cross-reactivity with pro-insulin, which may have confounded our findings. However, the results were not materially changed after exclusion of these studies in a sensitivity analysis. Third, the associations of fasting insulin concentrations with the outcomes of interest found in this meta-analysis were not completely independent of insulin resistance, because: *1*) not all studies detected insulin resistance status in addition to fasting insulin concentrations, and *2*) the effect of insulin resistance was impossible to be fully excluded from the models, whereas the exposure was fasting insulin concentrations. However, some included studies did adjust blood glucose concentrations in the model, which may have partially reduced this concern. In addition, we did not have enough information to assess the potential modifications by sex or study region (Eastern compared with Western countries).

Comparison with other studies

No published meta-analysis has directly related fasting insulin to the incidence of hypertension. The current study was the first, and the findings are consistent with those of a meta-analysis (38) published in 1992, which reported that fasting insulin concentrations were associated with both increased systolic BP and diastolic BP.

Also, the current study was the first meta-analysis to link fasting insulin concentrations to risk of stroke. The finding for stroke was mainly influenced by 2 studies, ie, Thacker et al's study (27) and Wieberdink et al's study (26). When one of them was excluded, the combined association was somewhat strengthened, ie, the pooled RR changed from 1.18 (95% CI: 0.87, 1.60) to 1.29 (95% CI: 0.87, 1.91) and 1.31 (95% CI: 0.96, 1.80), respectively. One possible explanation is that, only in these 2 studies, SBP, antihypertensive medication use, and ≥3 lipids were simultaneously overadjusted in the final model to give a spurious relation because hypertension and dyslipidemia may be intermediate variables in addition to strong confounders. In addition, for subtypes of stroke, the nonsignificant association was likely attributable to a small number of cases.

Several meta-analyses investigated the associations of fasting insulin concentrations with the risk of CHD. One meta-analysis (4) published in 1998 reported a pooled RR of CVD (including myocardial infarction, death from CHD, and/or electrocardiography abnormalities) of 1.18 (95% CI: 1.08, 1.29) with every 50-pmol/L increment in fasting insulin by combining 10 cohort studies and nested case-control studies. Another meta-analysis (39) found a positive association between fasting insulin concentrations and CVD mortality based on 7 prospective studies conducted in European countries. In addition, a meta-analysis published in 2007 included 14 prospective cohort studies and nested case-control studies (40), which found no significant association between fasting insulin concentrations and risk of CHD (mixed incidence and mortality).

Notably, a recent meta-analysis published in 2012 focusing on insulin resistance and incidence of combined cardiovascular events found no association between fasting insulin concentrations and risk of CHD (41). The null association found in that study may be explained by *1*) mixed prospective cohort studies and nested case-control studies, *2*) combined multiple health endpoints, and *3*) not having updated the findings from the Atherosclerosis Risk in Communities Study published in 2010 (21) with 960 CHD cases.

Potential mechanisms

Fasting insulin concentrations and risk of hypertension

Experimental studies suggest that insulin, a well-established inotropic agent (42), can increase cardiac output (43), blood volume through stimulating secretion of vasopressin (an antidiuretic) (44), and renal sodium retention (45). In addition, insulin can increase vascular tone by increasing basal concentrations of calcium in cytosol of vascular smooth muscle cells, stimulating the rennin-angiotensin system (46), and stimulating the secretion of endohelin-1 (47)—a vascular constrictor.

Although the likelihood of high BP causing elevated insulin concentrations cannot be excluded (48), the possibility should be small because changes in insulin concentrations usually precede the presence of obvious hypertension in metabolic diseases (49). In addition, a large body of evidence lends credence to an increase of BP by insulin (50, 51), but no existing evidence with respect to the underlying mechanism supports the idea that hypertension might cause hyperinsulinemia.

Fasting insulin concentrations and risk of CHD and stroke

In addition to traditional risk factors (eg, hypertension and dyslipidemia), insulin can increase risk of CHD and stroke through nontraditional CVD risk factors, including endothelial dysfunction, increased inflammation, and increased coagulation (52). First, insulin resistance is associated with endothelial dysfunction and the accumulation of reactive oxygen species in the vessel wall that help to initiate and maintain the atherosclerotic process. Second, insulin resistance can affect adipocyte function, giving rise to the generation of a number of inflammatory molecules (eg, C-reactive protein, complement C3), which play a crucial role in the atherosclerotic process. In addition, insulin resistance is associated with increased platelet activation and an increased concentration and activity of prothrombotic factors, which thereby ensures the presence of a prothrombotic milieu that could increase the risk of atherothrombotic events.

Summary

In conclusion, the meta-analysis of prospective cohort studies found that an elevated fasting insulin concentration or hyperinsulinemia was significantly associated with an increased risk of hypertension and CHD. Our study suggests that early ascertainment of fasting insulin may help clinicians identify those who are potentially at high risk of CVD.

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