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Letter to the Editor

Association between insulin-like growth factor-1 and cardiovascular disease risk: Evidence from a meta-analysis

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In recent years, insulin-like growth factor-1 (IGF-1) has been implicated in aging and development of age related diseases, like cardiovascular disease (CVD) and cancer. High serum IGF-I levels have been reported to increase many cancers risk, such as breast cancer [1], prostate cancer [2], thyroid cancer [3] and so on. IGF-1 is a 70-amino acid basic peptide hormone that is expressed in most tissues. IGF-1 is homologous to pro-insulin, primarily synthesized in liver and kidney, which reconciles and regulates the cell proliferation, apoptosis, migration, and differentiation [4–6]. Also, IGF-1 can regulate the vascular smooth muscle cell. Recent studies showed that the apoptosis of vascular smooth muscle cell could be a marker of unstable atherosclerotic plaques, leading to acute vascular events [7]. Several epidemiological studies had assessed the relationship between IGF-1 levels and risk of CVD, but the results were not consistent [8–19]. Based on the current understanding, we performed this systematic review and meta-analysis to get a more precise assessment of the impact of IGF-1 levels on CVD risk.

Search of PubMed, Web of Science, and Embase for articles on IGF-1 levels and CVD risk were conducted up to May 1st, 2015. The literature search had no regional limitation and no language limitation. The search terms and strategies were as follows: ("insulin-like growth factor-I", "insulin-like growth factor-1", "IGF-I" or "IGF-1") and ("CVD", "cardiovascular disease" or "cardiovascular") and ("cohort", "nested", "nested case–control", "prospective", or "cross-sectional"). We also checked the references of included studies and relevant reviews to find other eligible studies. Studies meeting the following selection criteria were included in the meta-analysis: (1) assessing the relationship between IGF-1 and risk of CVD; (2) prospective cohort studies, nested case–control studies, case–cohort studies, or cross-sectional studies; and (3) reporting relative risks (RRs) and 95% confidence intervals (95% CIs) for CVD risk according to IGF-1 levels. Case–control studies were all excluded. Studies were also excluded if they had overlapping data from other included studies.

Two investigators performed the data extraction independently. If there was any disagreement between the two investigators, it was resolved by discussion among all investigators. Data extracted from each study included the following information: first author's name, country, publication year, study design, number of participants, gender, types of CVD, time of follow-up, adjusted factors, and RRs with corresponding 95% CIs. If the included studies provided RRs with different adjusted factors, we used the most adjusted RRs in the meta-analysis. To assess the quality of the included studies, the Newcastle Ottawa scale (NOS) [20] was used, which generated a maximum of nine stars to each study. The NOS assessed the study quality on the selection of participants, the assessment of outcomes, and the comparability of participants. Quality was assigned according to the scores so that 7–9 stars indicated high quality, 4–6 stars for middle quality, and 0–3 stars for low quality.

We first determined the summary RRs of CVD comparing high versus middle categories in IGF-1 levels by gender, and then calculated the summary RRs of CVD comparing low versus middle categories in IGF-1 levels by gender. If the study only reported the RR for high versus low categories ($RR_{High\ versus\ Low}$) and RR for middle versus low categories ($RR_{Middle\ versus\ Low}$), we calculated out the relative RR for high versus middle categories of IGF-1 level ($RR_{High\ versus\ Middle}$), and calculated the standard error of the log $RR_{High\ versus\ Middle}$ as the square root of the sum of the variance of log $RR_{High\ versus\ Low}$ and log $RR_{Middle\ versus\ Low}$ for each of the studies [21]. Thirdly, we calculated the summary RRs of CVD comparing high versus low categories in IGF-1. Finally, we calculated the summary RRs of CVD per 1-SD increase in IGF-1 levels. Statistical heterogeneity was assessed with the I^2 statistic method where I^2 more than 50% indicated obvious heterogeneity [22]. Since there was obvious difference in the categories of IGF-1 levels and other baseline

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characteristics, we calculated the pooled RRs and 95% CIs using the random-effects model of meta-analysis [23]. Otherwise, we used the fixed-effects model [24]. Sensitivity analysis was performed by omitting one single study by turns to test the variability of the pooled RRs. Publication bias was assessed by visual inspection of the funnel plot. Asymmetry of the funnel plot was further assessed using Egger's regression test. A two-tailed $P < 0.05$ was considered statistically significant. Statistical analyses were performed with STATA version 12.0.

Finally, twelve studies [8–19] were included into this meta-analysis with 14,938 participants (Table 1). The main characteristics of the included studies were shown in Table 1. Among the twelve studies, six studies focused on the relationship between IGF-1 levels and CVD in mixed gender [8–11,15,18]; two studies reported the relationship between IGF-1 levels and CVD in male [17,19]; two studies [13,14] focused on the relationship between IGF-1 levels and CVD in female; one study [16] reported the relationship between IGF-1 levels and CVD in male and female; one study [12] reported the relationship between IGF-1 levels and CVD in male, female and mixed. Six studies [8,10,11,14,15,18] reported the relationship between IGF-1 levels per increase 1-SD and risk of CVD.

There was no obvious heterogeneity among the seven studies [9,11–13,16,18,19] reporting RRs comparing high versus middle categories of IGF-1 levels in overall, female and male by gender (overall $I^2 = 34.5\%$, female $I^2 = 0.0\%$, male $I^2 = 9.8\%$). Meta-analysis of these seven studies showed that higher IGF-1 levels were associated with increased risk of CVD in overall (summary RR = 1.16, 95% CI 1.04–1.28, P = 0.006), the similar to male (summary RR = 1.26, 95% CI 1.11–1.44, P = 0.001) (Fig. 1). For female, the meta-analysis did not found that

Table 1
The main characteristics of those 12 studies included into the meta-analysis.

Study	Country	Design	Participants	Follow-up	Adjusted factors	Quality	Gender
J.A.M.J.L.Janssen 1998	USA	Cross-sectional study	218 healthy persons (103 male, 115 female)	Not more than 6 months	Age	7	Mixed
Anders Juul 2002	Denmark	Nested case–control study	231 patients (male 168, female 63),374 control (male 261, female 113)	15 years	Age, sex, body mass index, smoking, menopause, diabetes, antihypertensive, diuretics, physical activity	6	Mixed
Ramachandran S.Vasan 2003	USA	Prospective cohort study	717 elderly individuals (67% female) 56 participants (35 female) developed congestive heart failure	5.2 years (maximum, 8.9 years)	Age, sex, diabetes, systolic blood pressure, hypertension treatment, smoking status, body mass index, total cholesterol–high-density lipoprotein cholesterol ratio, valve disease, prevalent atrial fibrillation, left ventricular hypertrophy on electrocardiography, and prevalent cardiovascular disease.	8	Mixed
Robert C. Kaplan 2007	USA	Case–cohort study	534 coronary events, 370 ischemic strokes and 1122 randomly selected participants (790 male 1236 female).	6.7 years for coronary events, 5.6 years for strokes, and 9.3 years for comparison subjects	Sex, race, age, treated hypertension, systolic blood pressure, smoking, cretonne, and HDL cholesterol	7	Mixed
Harald Jorn Schneider 2008	Germany	Cross-sectional study	6773 patients (4013 female, 2760 male)	1 year	Age, gender, body mass index, AST, GFR and smoking status	8	Mixed
John H. Page 2008	USA	Nested case–control study	245 cases and 482 controls	About 8 years	Age at blood draw, menopausal status, parents' history of myocardial infarction, current PMH use, duration of PMH use for more than 5 years, history of diabetes mellitus, history of hypertension, aspirin use, cigarette smoking, physical activity in metabolic equivalents — hours/week, mean daily alcohol intake, body mass index, plasma C-reactive protein and total HDL cholesterol ratio.	6	Female
Debbie A.Lawlor 2008	UK	Nested case–control study	167 cases and 333 controls	4 years	Age, adult social class, smoking, physical activity, waist: hip ratio, systolic blood pressure, fasting levels of high-density lipoprotein, triglyceride, glucose, Insulin and C-reactive protein	6	Female
Mikkel Andreassen 2009	Denmark	Prospective study	642 individuals (365 females, 277 males) aged 50–89 years	5 years	Age, sex, DM, atrial fibrillation, smoking status, NT-pro BNP, cholesterol and history of IHD, stroke, TIA or CHF	9	Mixed
Nele Friedricha 2010	Poland and Germany	Cross-sectional study	1848 participants (993 women and 855 men) aged 45–79 years,	About 5 years	Age, alcohol consumption, waist circumference, hypertension, and diabetes	8	Male
J.B. Ruidavets 2011	Northern Ireland and France	Nested case–control study	294 cases and 588 controls	5 years	Age, treatment for diabetes, hypertension, dyslipidemia, tobacco and alcohol consumptions, levels of physical activity and education, waist, circumference, systolic blood pressure, Apo lipoproteins A–I and B, C-reactive protein, ICAM-1, fibrinogen, glycemia and insulin.	6	Male
Sally L. Ricketts 2011	UK	Nested case–control study	1013 cases (654 male 359 female) and 2055 controls (1290 male 765 female)	6 years	Age, sex and enrolment date, waist circumference, smoking, diabetes, HDL-c, LDL-c, triglycerides, C-reactive protein, systolic and diastolic, blood pressure, IGFBP-3	7	Mixed
Daniel Carlzon 2014	Sweden	Prospective, population-based study	2901 elderly male (age 69–81 years), 367 participants experienced a CHD event	Median 5.1 years	Body mass index, Apo B/A4 ratio, quartile of physical activity, prevalent diabetes mellitus, hypertension, current smoking and history of cardiovascular disease	8	Male

(AST, aspartate aminotransferase; GFR, glomerular filtration rate; HDL, high-density lipoprotein; PMH, postmenopausal hormone; DM, diabetes mellitus; IHD, ischemic heart disease; TIA, transient ischemic attack; CHF, chronic heart failure; NT-pro BNP, N-terminal part of pro-brain natriuretic peptide; ICAM-1, intercellular adhesion molecule 1; LDL, low-density lipoprotein; IGFBP-3, insulin like growth factor binding protein 3; CHD, coronary heart disease.