Accepted Manuscript

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PII: S0026-0495(17)30326-8
DOI: doi:10.1016/j.metabol.2017.11.014
Reference: YMETA 53685

To appear in:

Received date: 19 March 2017
Accepted date: 20 November 2017

Please cite this article as: Da Young Lee, Eun-Jung Rhee, Yoosoo Chang, Chong Il Sohn, Ho-Cheol Shin, Seungho Ryu, Won-Young Lee , Impact of systemic inflammation on the relationship between insulin resistance and all-cause and cancer-related mortality. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Ymeta(2017), doi:10.1016/j.metabol.2017.11.014

Impact of systemic inflammation on the relationship between insulin resistance and all-cause and cancer-related mortality

Da Young Lee[a,b,¶], Eun-Jung Rhee[a,¶], Yoosoo Chang[c,d,e], Chong Il Sohn[f], Ho-Cheol Shin[g], Seungho Ryu[c,d,e,*], Won-Young Lee[a,*]

[a]Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

[b]Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University College of Medicine, Seoul, South Korea

[c]Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

[d]Center for Cohort Studies, Total Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

[e]Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, Seoul, South Korea

[f]Division of Gastroenterology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

[g]Department of Family Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

[¶]These authors contributed equally to this work.

[*]Corresponding author at:

Seungho Ryu, Department of Occupational and Environmental Medicine, Kangbuk Samsung

Hospital, Sungkyunkwan University School of Medicine, Samsung Main Building B2, 250, Taepyung-ro 2ga, Jung-gu, Seoul 04514, South Korea

Tel: +82-2-2001-5137; Fax: +82-2-2001-2049; E-mail: sh703.yoo@gmail.com

Won-Young Lee, Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 03181, South Korea

Tel: +82-2-2001-2579; Fax: +82-2-757-0436; E-mail: drlwy@hanmail.net

Word count: Abstract 272; Text 3,757

Number of tables and figures: 6

ABSTRACT

Background. Insulin resistance and inflammation play an important role in a variety of chronic diseases.

Objective. We investigated the influence of systemic inflammation on the relationship between insulin resistance and mortality risk in apparently healthy adults.

Methods. This study examined the mortality outcomes for 165,849 Koreans enrolled in a health-screening program. The subjects were divided into four groups according to their homeostatic model assessment of insulin resistance (HOMA-IR) and high-sensitivity C-reactive protein (hs-CRP) levels: group 0, HOMA-IR <75% and hs-CRP <2.0 mg/L; group 1, HOMA-IR ≥75% and hs-CRP <2.0 mg/L; group 2, HOMA-IR <75% and hs-CRP ≥2.0 mg/L; and group 3, HOMA-IR ≥75% and hs-CRP ≥2.0 mg/L. The Cox proportional hazard models were used to assess hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause, cardiovascular disease, and cancer-related mortality.

Results. During the follow-up period of 1,417,325.6 person-years, a total of 1,316 deaths (182 from cardiovascular disease) occurred. The multivariate-adjusted HRs for all-cause mortality were significantly higher in groups 2 (HR 1.40; 95% CI: 1.19–1.64) and group 3 (HR 1.68; 95% CI: 1.34–2.10) than that in group 0. For cardiovascular mortality, the sex-adjusted hazards were also significantly higher in groups 2 and 3 than that in group 0; however, this increased risk disappeared during multivariate analysis. Groups 2 and 3 had significantly higher risk for cancer-related mortality than group 0, with multivariate-adjusted hazard ratios of 1.48 (95% CI: 1.18–1.86) and 1.84 (95% CI: 1.35–2.51), respectively.

Conclusions. Systemic inflammation can be used to stratify the subjects according to the all-cause and cancer-related mortality risks, irrespective of the insulin-resistance status. And this tendency is most pronounced in cancer-related mortality.

Keywords:

High-sensitivity C-reactive protein; Inflammation; HOMA-IR; Insulin resistance; Mortality

Abbreviations:

CVD, cardiovascular disease; BMI, body mass index; HOMA-IR, high homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ICD-10, the International Classification of Diseases, 10th revision; HR, hazard ratio; CI, confidence interval; JUPITER, Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; NHANES, the Third National Health and Examination Survey; IL, Interleukin; TNF-α, tumor necrosis factor-α; CHD, coronary heart disease; IGF-I, insulin-like growth factor I

1. Introduction

Insulin resistance is known to be a causative factor in a variety of diseases, including type 2 diabetes, hypertension, cardiovascular disease (CVD), and various malignancies [1-4]. Furthermore, it was reported to be associated with all-cause, CVD, and cancer-related mortality in several studies [5-7]. However, the associations between insulin resistance and mortality have been inconsistently observed; for example, this association was observed only in individuals with body mass index (BMI) <25.2 kg/m^2, or a no association was found in other populations [5,8-10]. In addition, recently, a high homeostatic model assessment of insulin resistance (HOMA-IR) was reported to be associated with decreased all-cause and CVD mortality in individuals with obesity [10]. One pathogenic mechanism of action for insulin resistance is the promotion of atherosclerosis through inflammatory pathways [11,12].

Inflammation is known to play an important role in a variety of chronic diseases, including atherosclerosis [13,14]. In addition, cytokines may impair the insulin-signaling pathway by the phosphorylation of insulin receptors and their substrates [15]. High-sensitivity C-reactive protein (hs-CRP) is a widely used biomarker for inflammation and has been used to assess the risk of all-cause, CVD, and cancer-related mortality in previous studies [10,16-21].

Because of the close relationship between insulin resistance and inflammation, their interactive effects may help to predict future events, including CVD, cancer-related, and all-cause mortality. However, few studies have examined their interactions in mortality-risk assessment. This study investigates the influence of systemic inflammation on the relationship between insulin resistance and mortality in a population of apparently healthy adults.

2. Materials and Methods

2.1. Study Subjects

We conducted a retrospective longitudinal study. The study subjects consisted of adults, aged

20 years or older, who participated in the health-screening programs at the Kangbuk Samsung Hospital Total Healthcare Center (or its clinics) in Seoul and Suwon, South Korea. The Seoul Health Exam Center is located in the Jongno-Gu district in the center of Seoul. The Suwon Health Exam Center is located at Youngtong in Suwon, a developing city located about 30 miles from Seoul. More than 80% of study subjects were employees and family members of various industrial companies in South Korea. The health-screening program aims to promote the wellbeing of employees through regular medical checkups and increase the early detection of disease. The cost of these examinations is largely paid for by the employers. A considerable number of the examinees receive checkups annually or biannually.

We assessed the eligibility of 185,392 subjects who participated in the program between 2002 and 2006. A total of 19,543 subjects were excluded based on the following criteria: a history of diabetes (n = 7,344), stroke or ischemic heart disease (n = 1,352), or malignancy (n = 3,265); unknown cause of death (n = 1); or missing data, especially age, fasting glucose, HOMA-IR, or hs-CRP (n = 8,945). Because some subjects met multiple exclusion criteria, our final analysis was conducted with a total of 165,849 subjects (Supplementary Figure 1).

The subjects provided written informed consent for the use of their health-screening data in our research. The study was reviewed and approved by the Institutional Review Board of Kangbuk Samsung Hospital (KBS12089) and was carried out in accordance with the Helsinki Declaration of 1975.

2.2. Anthropometric and Laboratory Measurements

The subjects completed a structured questionnaire, addressing demographic characteristics and lifestyle habits such as smoking status, alcohol consumption, regular exercise, medical history, and medication use, derived from the fourth Korea National Health and Nutritional Examination Surveys [22-24], the Korean Genome and Epidemiology Study [25,26], the

Korean version of International Physical Activity Questionnaire short form [27], and the alcohol use disorders identification test: a Korean version [28], at each visit. Smoking status was categorized into the never, former, and current smokers categories. Alcohol consumption was categorized into the none, moderate (≤20 g/day), and high (>20 g/day) categories. The weekly frequency of moderate- and vigorous-intensity physical activity was also assessed. Regular exercise was defined as exercise of moderate- or vigorous-intensity that occurred at least three times a week.

The BMI of the subjects was calculated as weight in kilograms divided by the square of height in meters. Individuals with BMI ≥25 kg/m^2 were classified as obese according to the revised Asia–Pacific criteria of obesity, as suggested by the World Health Organization Western Pacific Region in 2000 [29].

Sitting blood pressure (BP) was measured using standardized sphygmomanometers after 5 minutes of rest by trained nurses. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, self-reported history of hypertension, or current use of antihypertensive medications.

Venous blood samples were collected in the morning (8–9 am) after an overnight fast of at least 8 hours. Biochemical analyses were performed at the Laboratory Medicine Department of the Kangbuk Samsung Hospital in Seoul. Serum concentrations of glucose, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) were measured using Bayer Reagent Packs on an automated chemical analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). Serum hs-CRP levels were analyzed by nephelometry, using a BNII nephelometer (Dade Behring, Deerfield, IL). Serum uric acid levels were measured using an Advia 1650 Autoanalyzer. Serum insulin levels were determined by

immunoradiometric assay using a DIAsource Kit (DIAsource ImmunoAssay SA, Louvain-la-Neuve, Belgium). Insulin resistance was measured using HOMA-IR and was obtained by applying the following formula [30,31]: HOMA-IR = fasting insulin (IU/mL) × fasting blood glucose (mmol/L)/22.5.

Metabolic syndrome was defined as the presence of three or more of the following risk factors [32]: (1) abdominal obesity, defined as a waist circumference ≥90 cm in men or ≥85 cm in women [29]; (2) impaired fasting glucose, defined as fasting glucose ≥100 mg/dL; (3) high triglycerides, defined as triglycerides >150 mg/dL or use of an antilipidemic drug; (4) low HDL-C, defined as HDL-C <50 mg/dL in men, <40 mg/dL in women, or use of an antilipidemic drug; and (5) BP ≥130/85 mmHg or use of an antihypertensive agent. Subjects who graduated high school were defined as subjects with higher education.

All examinations were conducted at the Kangbuk Samsung Hospital Health Screening Center clinics in Seoul and Suwon. The Laboratory Medicine Department of the Kangbuk Samsung Hospital is accredited by the Korean Society of Laboratory Medicine and the Korean Association of Quality Assurance for Clinical Laboratories, and participates in the College of American Pathologists Survey Proficiency Testing.

2.3. Mortality Follow-up

The vital status of study subjects was identified through linkage with the nationwide death-certificate data from the Korea National Statistical Office until December 31, 2012. The National Statistical Office maintains the death records of all Koreans. Abstractors coded the causes of death according to the International Classification of Diseases, 10th revision (ICD-10). Cancer-related mortality was defined by ICD-10 codes, C00–C97, and CVD mortality was defined as ICD-10 codes, I00–I99 [33]. For mortality cases, person-years were calculated as the sum of the follow-up duration from baseline until the date of death. For survivors,

person-years were calculated as the sum of the follow-up duration from baseline until December 31, 2012.

2.4. Statistical Analyses

First, the subjects were stratified into quartiles according to baseline HOMA-IR (called Q1, Q2, Q3, and Q4). Data are presented as means (standard deviations) and percentages. The baseline characteristics of subjects were compared using analysis of variance for continuous variables and chi-square tests for categorical variables. The distribution of continuous variables was evaluated, and right-skewed variables (TG, AST, ALT, GGT, HOMA-IR, and hs-CRP) were log transformed for the one-way analysis of variance. Post-hoc multiple comparison analysis was performed with Bonferroni correction.

To assess hazard ratios (HRs) and 95% confidence intervals (CIs) for the all-cause, CVD, and cancer-related mortalities, the Cox proportional hazard models were performed. We used age as the time-scale where subjects enter the analysis at their age at the time of their first health checkup exam (left truncation) and exit at their age on the date of death or on December 31, 2012. Initially, each mortality outcome was adjusted for sex. Then, we used two additional models to adjust for confounders: model 1 was adjusted for sex, study center (Suwon or Seoul), year of screening examination, smoking status, alcohol intake, regular exercise, BMI, education level, and history of hypertension. Model 2 was adjusted for the variables in model 1 plus hs-CRP, TC, HDL-C, and TG levels. The reference group was Q1. To determine the linear risk trends across HOMA-IR quartiles, we used the category rank as a continuous variable in the regression models. Kaplan-Meier survival analyses were performed for all-cause, CVD, and cancer-related mortality according to HOMA-IR quartiles. Further, we repeated the abovementioned Cox analysis according to hs-CRP quartiles with the same method, except HOMA-IR instead of hs-CRP levels in model 2. We tested the proportional

hazards assumption by using graphs of estimated log (-log) survival. To avoid multicollinearity, we assessed the variable inflation factor (VIF) for all the covariates included in each of the regression models. All variables had a VIF less than 2.0, indicating no relevant multicollinearity among covariates.

Additionally, after dividing into two groups according to sex, current smoking, alcohol intake of 20 g/day, vigorous-exercise frequency of 3 times per week, or obesity, we evaluated HRs and 95% CIs for the all-cause, CVD, and cancer-related mortality according to HOMA-IR quartiles using Cox proportional hazard models with HOMA-IR Q1 as the reference group. We adjusted for sex, study center, year of screening examination, smoking status, alcohol intake, regular exercise, BMI, education level, and history of hypertension in this subgroup analysis. Interactions between subgroups were tested using the likelihood ratio tests comparing models with and without multiplicative interaction terms.

Cubic plots were constructed to estimate the relationship between HOMA-IR levels and HRs for the all-cause, CVD, and cancer-related mortality using knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of HOMA-IR distribution. Models were adjusted for sex, study center, year of screening examination, smoking status, alcohol intake, physical activity, education level, BMI, and history of hypertension.

Additionally, we adopted a threshold of 2 mg/L for hs-CRP levels, as used in the "Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)" study [34]. Subjects in the top quartile of the HOMA-IR distribution values (HOMA-IR ≥2.31) were considered to be insulin resistant as reported in previous studies [35-37]. The subjects were divided into four groups according to the HOMA-IR and hs-CRP levels as follows: group 0, HOMA-IR <75% and hs-CRP <2.0 mg/L; group 1, HOMA-IR ≥75% and hs-CRP <2.0 mg/L; group 2, HOMA-IR <75% and hs-CRP ≥2.0 mg/L; and group 3, HOMA-IR ≥75% and hs-CRP ≥2.0 mg/L.

The previously described Cox proportional hazard models were repeated. We evaluated sex-adjusted HRs (95% CIs) and multivariate-adjusted HRs (95% CIs; as in model 2) for the all-cause, CVD, and cancer-related mortality. Group 0 was used as the reference group. Furthermore, Kaplan-Meier survival analyses were performed. Interactions between HOMA-IR and hs-CRP levels for each of the three indicated mortalities were tested using the likelihood ratio tests comparing models with and without multiplicative interaction terms in the Cox-proportional hazards regression models.

STATA software version 13.1 (Stata, College Station, TX) was used for statistical analysis. A *p* value of <.05 was considered to be statistically significant. The *p* values were corrected using the Bonferroni's method for multiple testing. We investigated all data retrospectively.

3. Results

The baseline characteristics are described in Table 1. Age, BMI, BP, glucose, TC, LDL-C, TG, hs-CRP levels, obesity, metabolic syndrome, and hypertension increased, and HDL-C levels and regular exercise decreased as HOMA-IR quartiles increased.

The mean follow-up period was 8.54 ± 1.42 years (interquartile range 7.36–9.69). During the follow-up period of 1,417,325.6 person-years, a total of 1,316 deaths (182 from CVD) occurred. Table 2 shows HRs and 95% CI values for the all-cause, CVD, and cancer-related mortality according to HOMA-IR quartiles. The risk for all-cause mortality for subjects in Q4 was significantly higher than that for subjects in Q1 in model 1, with an HR of 1.21 (95% CI: 1.02–1.43). Likewise, in subgroup analysis, significantly higher risk for all-cause mortality was observed in subjects in Q4 than that for those in Q1 (Supplementary Table 1). When examining CVD mortality, there were no significant differences in HRs across HOMA-IR quartiles; likewise, subgroup analysis revealed no differences (Table 2 and Supplementary Table 2). The risk for cancer-related mortality was significantly increased for subjects in Q4

versus that for those in Q1, with an HR of 1.34 (95% CI: 1.06–1.70). This significantly increased risk was also observed after adjustment for hs-CRP levels and lipid profiles in model 2 (Table 2). When we conducted subgroup analysis, significantly higher risk for cancer-related mortality was observed in subjects from Q4 versus that for those in Q1 (Supplementary Table 3).

In cubic spline plots, gradual increases of HRs for all-cause and cancer-related mortality were seen until HOMA-IR reached a value near 3. Above this level, steeper increases were observed (Figure 1).

When we conducted Cox analysis of hs-CRP quartiles, subjects in Q4 showed significantly increased risk for all-cause and cancer-related mortality compared with that for those in Q1 (Table 3).

As shown in Table 4, when we divided the subjects according to HOMA-IR levels in the 75th percentile and hs-CRP levels of 2.0 mg/L, the sex-adjusted HRs for all-cause mortality in groups 2 and 3 with hs-CRP levels of ≥2.0 mg/L were 1.45 (95% CI: 1.24–1.71) and 1.59 (95% CI: 1.28–1.97), respectively. These significantly increased risks were also observed after multivariate-adjusted Cox analysis. When examining CVD mortality, the sex-adjusted HRs for groups 2 and 3 were 1.51 (95% CI: 1.00–2.30) and 2.06 (95% CI: 1.23–3.45), respectively (Table 4). However, this increased risk disappeared in multivariate analysis. Groups 2 and 3 had significantly higher risk for cancer-related mortality compared to group 0 with their multivariate-adjusted HRs being 1.48 (95% CI: 1.18–1.86) and 1.84 (95% CI: 1.35–2.51), respectively (Table 4). In Kaplan-Meier survival analyses for the four groups, subjects in groups 2 and 3 with increased hs-CRP levels showed the lowest survival rates (Figure 2). No interaction between HOMA-IR and hs-CRP levels was observed for the all-cause, CVD, and cancer–related mortality (*p* values were 0.772, 0.219, and 0.925, respectively).

4. Discussion

In this large population-based cohort of apparently healthy adults, the subjects in the highest HOMA-IR or hs-CRP quartile, Q4, had significantly higher risks for all-cause and cancer-related mortalities than those in Q1. Further, this tendency became more pronounced when waist circumference was added, indicating central obesity as a covariate in the Cox analysis conducted in 80,168 participants who underwent waist circumference measurements, as shown in Supplementary Table 4 and 5. While the subjects with insulin resistance (HOMA-IR ≥75%) and low hs-CRP levels (<2.0 mg/L) showed no increased risk for mortality despite high insulin-resistance, the subjects with both insulin resistance (HOMA-IR ≥75%) and high hs-CRP levels (≥2.0 mg/L) had increased HRs for all-cause and cancer-related mortalities. In other words, systemic inflammation status could help to stratify subjects with the same insulin-resistance status based on their future all-cause and cancer-related mortality risks.

The predictive effects of hs-CRP levels on the all-cause and CVD mortalities have been demonstrated in various populations, such as the Third National Health and Examination Survey (NHANES) study in Koreans, older German adults, and Japanese subjects [16,38,39]. Moreover, the predictive value of the hs-CRP levels combined with HDL-C levels, as well as the interactions between hs-CRP and traditional risk factors in the prediction of all-cause mortality have been investigated elsewhere [20,39].

Previous studies have reported that inflammatory responses play a crucial role in development of insulin resistance through innate immune function mediated by macrophages and adaptive immune system mediated by T lymphocyte [40,41]. Interleukin (IL)-1β and interferon-γ which are inflammatory cytokines are found to modulate insulin signaling [40-42], whereas anti-inflammatory cytokines, such as IL-4 and IL-10 are known to improve insulin sensitivity [40,43]. Conversely, hyperinsulinemia itself can induce increases in the inflammatory cytokines, IL-6 and tumor necrosis factor-α (TNF-α), which in turn promote

insulin resistance [15,44,45]. In a population-based study, Shai et al. reported the combined effects of soluble TNF-α receptor II and glycemic status; individuals with higher levels of both soluble TNF-α receptor II and hemoglobin A1c had the most increased relative risk for coronary heart disease (CHD) events among diabetic women [46]. However, this study was conducted in subjects who were already at a high risk for CHD, given that >20% had a previous history of myocardial infarction, and nearly half had hypertension or dyslipidemia. Therefore, our study is meaningful in that the combined effect of inflammation and insulin resistance on predicting mortality risk was demonstrated in much younger adults after excluding the subjects with diabetes or previous history of CVD.

Another interesting finding of our study is that cancer-related mortality was significantly greater for subjects with increased hs-CRP levels or insulin resistance. An association between high levels of insulin-like growth factor 1 (IGF-I) and/or insulin and an increased risk for several malignancies have been reported [47-49]. This can be explained by the fact that insulin and IGF-I inhibit apoptosis and enhance cellular proliferation, resulting in accumulation of genetic mutations and carcinogenesis [47]. Further, previous epidemiological studies show association of chronic inflammation with increased risk of malignancy and poor prognosis, such as distant metastasis, tumor size, node metastasis, and tumor recurrence [50,51]. Furthermore, in a study using the NHANES data, high levels of hs-CRP in men corresponded to an increased risk of cancer-related mortality (HR of 2.90 [95% CI: 1.52–5.53]) [21]. Pro-survival effects of TNF-α on cancer cells, overstimulation of the Janus kinase/signal transducers and activators of transcription pathway by IL-6, and matrix metalloproteinases were thought to mediate it [52,53]. Previous study reported anti-neoplastic property of adiponectin through an insulin-sensitizing and anti-inflammatory effect [54]. Significant decrease in adiponectin level was expected in group 3 in our study. However, as this study is analyzed from a dataset of a health screening program, we do not have any serum

samples available that could measure adiponectin retrospectively.

Even though insulin resistance and systemic inflammation are well-known risk factors for CVD and mortality, our study found no significant associations with CVD mortality. The multivariate-adjusted HRs for hs-CRP Q3 and 4 lost significance after additionally adjusting HOMA-IR and lipid profiles (Table 3), and significance of HRs for group 2 and 3 also disappeared in multivariate analysis (Table 4). The impact of TG and HDL-C, as well as LDL-C, on metabolic disorders has been found in previous studies [20,55,56]. Increased TG levels activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and increase inflammatory molecules, and can predict CAD risk [56]. In a large epidemiologic study of a Korean population, elevated CRP and low HDL-C levels were found to jointly predict mortality [20]. Such interactive relationship between inflammation and lipid profiles could explain our findings. It is also possible that several interventions to decrease CVD risk, such as antihypertensive medications or statins taken during the study period, could have influenced the CVD mortality data in our study. In addition, the relatively young age of the study population and low absolute mortality rates may have also contributed to our observed results. A previous study conducted in the same cohort showed a significantly increased risk for CVD mortality [16]; however, unlike the previous study, in the current study we excluded subjects with diabetes at baseline or subjects with a previous history of CVD.

Cutoff-points of HOMA-IR and hs-CRP levels were determined by considering more established parameters. Like many previous studies, we defined the top quartile of HOMA-IR distribution values (≥2.31 in our study) as insulin resistance [35-37]. In case of hs-CRP, the distribution of hs-CRP concentration is clearly low, with the median being 0.4 mg/L (interquartile range: 0.1–1.1 mg/L). Lower hs-CRP values of Asians than white populations were also observed in previous studies, and thought to be related to differences in genetic factors, BMI, diet, and lifestyle [16,19,20,57]. However, given that the sample size of prior

studies conducted in Asians were small, and that they were conducted in only one ethnicity [16,19,20], it is not suitable to be used in clinical researches. Therefore, we set an hs-CRP cutoff-point of 2.0 mg/L (75th percentile value) instead of 1.1 mg/L, as used in the multinational JUPITER study conducted at 1,315 sites in 26 countries [34]. When we conducted the Cox analysis again after defining an hs-CRP cutoff-point of 1.0 mg/L, similar findings to that observed with the cutoff-point of 2.0 mg/L were found as shown in Supplementary table 6.

To the best of our knowledge, this is the first study to demonstrate the relationship between insulin resistance and systemic-inflammation status on mortality risk. However, several limitations should be considered. First, this was a retrospective study based on a health screening program. Since we simply analyzed the data from a selected population, the study subjects were biased towards individuals with access to health care. Therefore, it is difficult to generalize the findings of our study to other populations. However, despite this selection bias, we were provided with death records for 165,849 individuals from a single ethnic group, as well as detailed clinical and biochemical assessments, which allowed us to perform various adjustments for potential confounders. Second, we did not assess the exact type or stage of malignancy that resulted in mortality. Finally, we used HOMA-IR as measurement of insulin resistance instead of the euglycemic-hyperinsulinemic clamp, the criterion standard method. The euglycemic-hyperinsulinemic clamp method is too costly and technically demanding to be used in clinical practice, but HOMA-IR has been demonstrated to have a good correlation with results derived from the clamp method. HOMA-IR mainly reflects hepatic insulin resistance and does not account for the total effects of insulin resistance [31]. However, among the parameters of insulin resistance, the most widely used and well-known is that of HOMA-IR, which is used as a modified definition of the metabolic syndrome [30,32,58], and is regarded as an appropriate method for estimating insulin resistance in epidemiologic studies

[31]. Therefore, we defined the top quartile of HOMA-IR distribution values as insulin resistance like many previous studies [35-37]. When we divided the subjects according to fasting glucose and insulin quartiles, subjects from insulin-quartile 4 had significantly higher hazards for all-cause and cancer-related mortality than that in those from quartile 1 (Supplementary Table 7 and 8).

In conclusion, systemic-inflammation status, as determined by hs-CRP levels of 2.0 mg/L, can stratify the subjects according to the all-cause and cancer-related mortality risks, irrespective of the insulin-resistance status. Therefore, the all-cause and cancer-related mortality risks according to HOMA-IR may be reclassified by hs-CRP levels, and this tendency is most pronounced in cancer-related mortality.

Acknowledgements

This study was supported by a grant from Samsung Biomedical Research Institute (SBRI) (http://www.sbri.or.kr). This funder had no role in the study design, data collection and analysis, the decision to publish, or preparation of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

D.Y.L. and E.J.R. contributed to the study design, statistical analyses, and interpretation of results, and wrote the manuscript. Y.C. contributed to statistical analyses and interpretation of results. C.I.S. and H-C S. contributed to the discussion. S.R. contributed to the study design, statistical analyses, interpretation of results, and reviewed and edited the manuscript. W-Y.L. contributed to the study design, interpretation of results, and reviewed and edited the manuscript.

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Table 1 - Baseline characteristics of study subjects by HOMA-IR quartiles

Characteristics	Total	HOMA-IR quartiles				*P* for trend
		Q1 (0.23–1.38)	Q2 (1.39–1.78)	Q3 (1.79–2.30)	Q4 (2.31–32.7)	
Number	165,849	41,467	41,463	41,464	41,455	
Age (years)*	39.5 (9.2)	39.3 (8.9)	39.4 (9.2)	39.5 (9.2)	39.7 (9.3)	<0.001
BMI (kg/m^2)*	23.5 (3.1)	22.2 (2.6)	22.9 (2.7)	23.7 (2.9)	25.2 (3.3)	<0.001
Male (%)	58.0	57.6	55.4	57.3	61.8	<0.001
Current smoker (%)	27.9	29.5	26.4	26.7	29.1	0.315
Alcohol intake >20 g/day (%)	13.8	13.1	12.7	13.5	15.8	<0.001
Regular exercise (%)‡	15.2	17.6	16.0	14.4	12.6	<0.001
Obesity (%)¶	29.8	14.1	21.7	31.9	51.6	<0.001
Higher education (%)§	68.1	66.6	67.8	69.1	69.0	<0.001
Metabolic syndrome (%)	14.5	3.6	7.9	13.9	32.5	<0.001
Hypertension (%)	16.4	10.9	13.5	16.6	24.8	<0.001
Systolic BP (mmHg)*	114.6 (14.6)	111.6 (13.5)	113.4 (14.1)	115.0 (14.4)	118.6 (15.4)	<0.001
Diastolic BP (mmHg)*	74.3 (10.4)	72.2 (9.8)	73.3 (10.0)	74.5 (10.2)	77.1 (10.7)	<0.001

Glucose (mg/dL)*	92.4 (8.9)	87.4 (7.8)	91.2 (7.7)	93.3 (7.9)	97.9 (8.8)	<0.001
Uric acid (mg/dL)*	5.3 (1.4)	5.1 (1.3)	5.2 (1.4)	5.3 (1.4)	5.6 (1.5)	<0.001
Total cholesterol (mg/dL)*	195.8 (35.2)	193.7 (34.1)	193.6 (34.9)	195.4 (35.1)	200.6 (36.3)	<0.001
LDL-C (mg/dL)*	113.7 (29.4)	110.8 (28.6)	111.7 (29.0)	113.9 (29.2)	118.2 (30.3)	<0.001
HDL-C (mg/dL)*	55.8 (12.2)	58.3 (12.8)	56.8 (12.3)	55.2 (11.8)	52.9 (11.2)	<0.001
Triglycerides (mg/dL)†	107 (75–157)	89 (66–125)	99 (71–141)	111 (79–161)	136 (94–199)	<0.001
AST (U/L)†	23 (19–27)	22 (19–26)	22 (19–26)	23 (19–27)	24 (20–30)	<0.001
ALT (U/L)†	21 (16–31)	19 (15–26)	20 (15–28)	22 (16–31)	27 (18–41)	<0.001
GGT (U/L)†	19 (12–34)	16 (11–25)	17 (11–29)	20 (12–34)	27 (15–49)	<0.001
hs-CRP (mg/L)†	0.4 (0.1–1.0)	0.3 (0.1–0.8)	0.4 (0.1–0.8)	0.5 (0.1–1.0)	0.6 (0.3–1.3)	<0.001

Data are *means (standard deviation), †medians (interquartile range), or percentages.

One-way analysis of variance for continuous variables and chi-square tests for categorical variables were used to compare the characteristics of the study subjects at baseline, and the right-skewed variables (triglycerides, AST, ALT, GGT, and hs-CRP) were log transformed for the one-way analysis of variance. Post-hoc multiple comparison analysis was performed with the Bonferroni correction.

HOMA-IR, homeostasis model assessment of insulin resistance; BMI, body mass index; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate transaminase; ALT, alanine aminotransferase; GGT, gamma-glutamyl

transpeptidase; hs-CRP, high-sensitivity C-reactive protein.

‡ Moderate or vigorous intensity exercise of ≥3 times per week.

¶ BMIs of ≥25 kg/m^2

§ Subjects who graduated high school

Table 2 - Risk of death from all causes, cardiovascular disease, and cancer by HOMA-IR quartiles

	Person-years	Number of events	Mortality rate (100,000 person-years)	Sex-adjusted HRs (95% CI)	Multivariate-adjusted HRs* (95% CI)	
					Model 1	Model 2
All-cause mortality						
Q1 (0.23–1.39)	377,626.5	358	94.8	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (1.39–1.79)	350,385.9	314	89.6	0.96 (0.83–1.12)	1.04 (0.89–1.22)	1.06 (0.90-1.23)
Q3 (1.79–2.31)	348,795.1	299	85.7	0.93 (0.80–1.08)	1.04 (0.88–1.22)	1.05 (0.89-1.23)
Q4 (2.31–32.7)	340,518.1	345	101.3	1.05 (0.91–1.22)	1.21 (1.02–1.43)	1.20 (1.01-1.43)
P for trend				0.650	0.041	0.053
Cardiovascular mortality						
Q1 (0.23–1.39)	377,626.5	48	12.7	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (1.39–1.79)	350,385.9	42	12.0	0.98 (0.64–1.48)	0.95 (0.62–1.46)	0.92 (0.60-1.41)
Q3 (1.79–2.31)	348,795.1	48	13.8	1.12 (0.75–1.68)	1.03 (0.67–1.57)	0.98 (0.64-1.50)
Q4 (2.31–32.7)	340,518.1	44	12.9	1.02 (0.68–1.54)	0.81 (0.51–1.29)	0.75 (0.47-1.19)
P for trend				0.746	0.467	0.288
Cancer-related mortality						

Q1 (0.23–1.39)	377,626.5	168	44.5	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (1.39–1.79)	350,385.9	151	43.1	0.98 (0.78–1.21)	1.06 (0.85–1.33)	1.10 (0.87-1.38)
Q3 (1.79–2.31)	348,795.1	156	44.7	1.02 (0.82–1.27)	1.16 (0.92–1.45)	1.20 (0.95-1.51)
Q4 (2.31–32.7)	340,518.1	178	52.3	1.14 (0.93–1.41)	1.34 (1.06–1.70)	1.40 (1.10-1.78)
P for trend				0.193	0.014	0.006

Cox proportional hazard models using age as a timescale were used to estimate hazard ratios and 95% confidence intervals. Right-skewed variables (triglycerides and hs-CRP) were log transformed for the analysis. Model 1 was adjusted for sex, study center, year of health-screening examination, smoking status, alcohol intake, regular exercise, body mass index, education level, and history of hypertension. Model 2 is the same as model 1, plus an adjustment for high-sensitivity C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, and triglycerides.

HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; CI, confidence interval.

Table 3 - Risk of death from all causes, cardiovascular disease, and cancer by high-sensitivity C-reactive protein quartiles

	Person-years	Number of events	Mortality rate (100,000 person-years)	Sex-adjusted HRs (95% CI)	Multivariate-adjusted HRs* (95% CI)	
					Model 1	Model 2
All-cause mortality						
Q1 (<0.3 mg/L)	425,552.8	234	55.0	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (0.3–0.4 mg/L)	285,530.0	212	74.3	0.93 (0.78–1.13)	0.96 (0.79–1.15)	0.98 (0.81–1.18)
Q3 (0.5–1.0 mg/L)	380,881.5	393	103.2	1.12 (0.95–1.32)	1.15 (0.97–1.36)	1.18 (0.99–1.40)
Q4 (≥1.1 mg/L)	325,361.4	477	146.6	1.38 (1.17–1.62)	1.37 (1.16–1.62)	1.40 (1.18–1.66)
P for trend				<0.001	<0.001	<0.001
Cardiovascular mortality						
Q1 (<0.3 mg/L)	425,552.8	25	5.9	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (0.3–0.4 mg/L)	285,530.0	16	5.6	0.67 (0.65–1.25)	0.64 (0.34–1.21)	0.63 (0.33–1.18)
Q3 (0.5–1.0 mg/L)	380,881.5	67	17.6	1.80 (1.13–2.86)	0.65 (1.02–2.66)	1.58 (0.98–2.57)
Q4 (≥1.1 mg/L)	325,361.4	74	22.7	1.99 (1.25–3.17)	1.64 (1.01–2.67)	1.58 (0.96–2.58)
P for trend				<0.001	0.002	0.005
Cancer–related mortality						

Q1 (<0.3 mg/L)	425,552.8	102	24.0	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (0.3–0.4 mg/L)	285,530.0	122	42.7	1.18 (0.91–1.54)	1.19 (0.91–1.55)	1.24 (0.95–1.61)
Q3 (0.5–1.0 mg/L)	3480,881.5	182	47.8	1.13 (0.88–1.44)	1.13 (0.88–1.46)	1.19 (0.93–1.54)
Q4 (≥1.1 mg/L)	325,361.4	247	75.9	1.56 (1.23–1.97)	1.52 (1.19–1.95)	1.59 (1.14–1.88)
P for trend				<0.001	0.001	<0.001

Cox proportional hazard models using age as a timescale were used to estimate hazard ratios and 95% confidence intervals. Right-skewed variables (triglycerides and hs-CRP) were log transformed for the analysis. Model 1 was adjusted for sex, study center, year of health-screening examination, smoking status, alcohol intake, regular exercise, body mass index, education level, and history of hypertension. Model 2 is the same as model 1, plus an adjustment for HOMA-IR, total cholesterol, high-density lipoprotein cholesterol, and triglycerides.

HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; CI, confidence interval.

Table 4 - Risk of death from all causes, cardiovascular disease, and cancer by HOMA-IR levels in the 75th percentile and hs-CRP levels of 2.0 mg/L

	Person-years	Number of events	Mortality rate (100,000 person-years)	Sex-adjusted HRs (95% CI)	Multivariate-adjusted HRs* (95% CI)
All-cause mortality					
HOMA-IR <75%* & hs-CRP <2.0 mg/L (group 0)	968,190.5	779	80.5	1.00 (reference)	1.00 (reference)
HOMA-IR ≥75%* & hs-CRP <2.0 mg/L (group 1)	287,097.3	251	87.4	1.05 (0.91–1.22)	1.15 (0.99–1.34)
HOMA-IR <75%* & hs-CRP ≥2.0 mg/L (group 2)	108,616.9	192	176.8	1.45 (1.24–1.71)	1.40 (1.19–1.64)
HOMA-IR ≥75%* & hs-CRP ≥2.0 mg/L (group 3)	53,420.9	94	176.0	1.59 (1.28–1.97)	1.68 (1.34–2.10)
Cardiovascular mortality					
HOMA-IR <75%* & hs-CRP <2.0 mg/L (group 0)	968,190.5	109	11.3	1.00 (reference)	1.00 (reference)
HOMA-IR ≥75%* & hs-CRP <2.0 mg/L (group 1)	287,097.3	27	9.4	0.82 (0.54–1.25)	0.70 (0.45–1.08)
HOMA-IR <75%* & hs-CRP ≥2.0 mg/L (group 2)	108,616.9	29	26.7	1.51 (1.00–2.30)	1.34 (0.87–2.04)
HOMA-IR ≥75%* & hs-CRP ≥2.0 mg/L (group 3)	53,420.9	17	31.8	2.06 (1.23–3.45)	1.48 (0.86–2.56)
Cancer-related mortality					
HOMA-IR <75%* & hs-CRP <2.0 mg/L (group 0)	968,190.5	376	38.8	1.00 (reference)	1.00 (reference)

HOMA-IR ≥75%* & hs-CRP <2.0 mg/L (group 1)	287,097.3	128	44.6	1.11 (0.91–1.36)	1.22 (0.98–1.50)
HOMA-IR <75%* & hs-CRP ≥2.0 mg/L (group 2)	108,616.9	99	91.2	1.54 (1.23–1.93)	1.48 (1.18–1.86)
HOMA-IR ≥75%* & hs-CRP ≥2.0 mg/L (group 3)	53,420.9	50	93.6	1.73 (1.29–2.32)	1.84 (1.35–2.51)

* The cutoff value of HOMA-IR of 75% was 2.31 mg/L.

Cox proportional hazard models using age as a timescale were used to estimate hazard ratios and 95 % confidence intervals. Right-skewed variables (triglycerides and hs-CRP) were log transformed for the analysis. Multivariate-adjusted model was adjusted for sex, study center, year of health-screening examination, smoking status, alcohol intake, regular exercise, body mass index, education level, history of hypertension, total cholesterol, high-density lipoprotein cholesterol, and triglycerides.

HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein; HR, hazard ratio; CI, confidence interval.

Figure Legends

Fig. 1 - Multivariate-adjusted hazard ratios for all-cause mortality (A), cardiovascular mortality (B), and cancer-related mortality (C) by HOMA-IR level.

Curves represent adjusted hazard ratios (solid lines) and 95% confidence intervals (dotted lines) for all-cause, cardiovascular, and cancer-related mortality based on restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the HOMA-IR distribution. Models were adjusted for sex, study center, year of health-screening examination, smoking status, alcohol intake, physical activity, education level, body mass index, history of hypertension, total cholesterol, high-density lipoprotein cholesterol, and triglycerides.

Fig. 2 - Kaplan-Meier survival curves of outcomes for all-cause mortality (A), cardiovascular mortality (B), and cancer-related mortality (C) according to the 75th percentile of HOMA-IR and the baseline high-sensitivity C-reactive protein levels of 2.0 mg/L. Models were adjusted for sex, study center, year of health-screening examination, smoking status, alcohol intake, physical activity, education level, body mass index, history of hypertension, total cholesterol, high-density lipoprotein cholesterol, and triglycerides. For the risk of all-cause and cancer-related mortality, groups 0 and 1 were statistically different from groups 2 and 3 (p<0.001, for both mortalities).

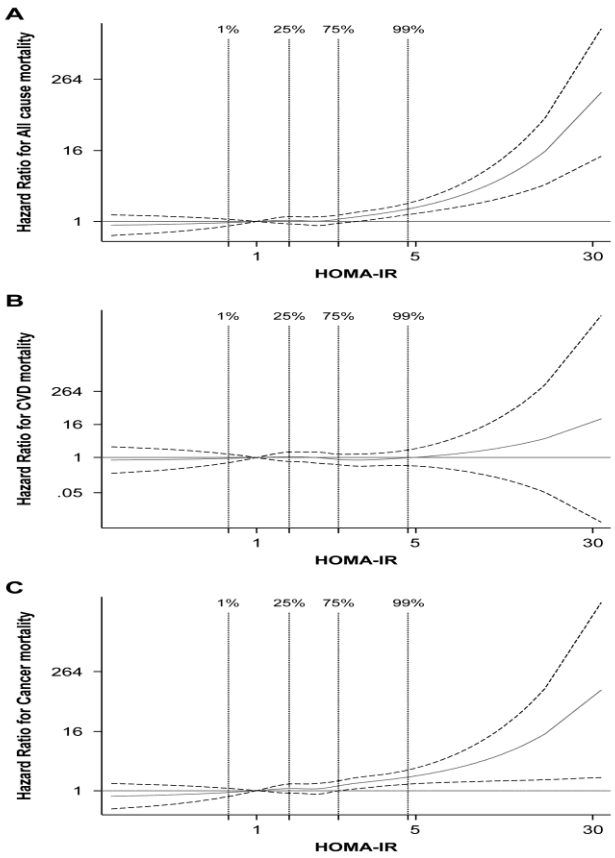

Figure 1

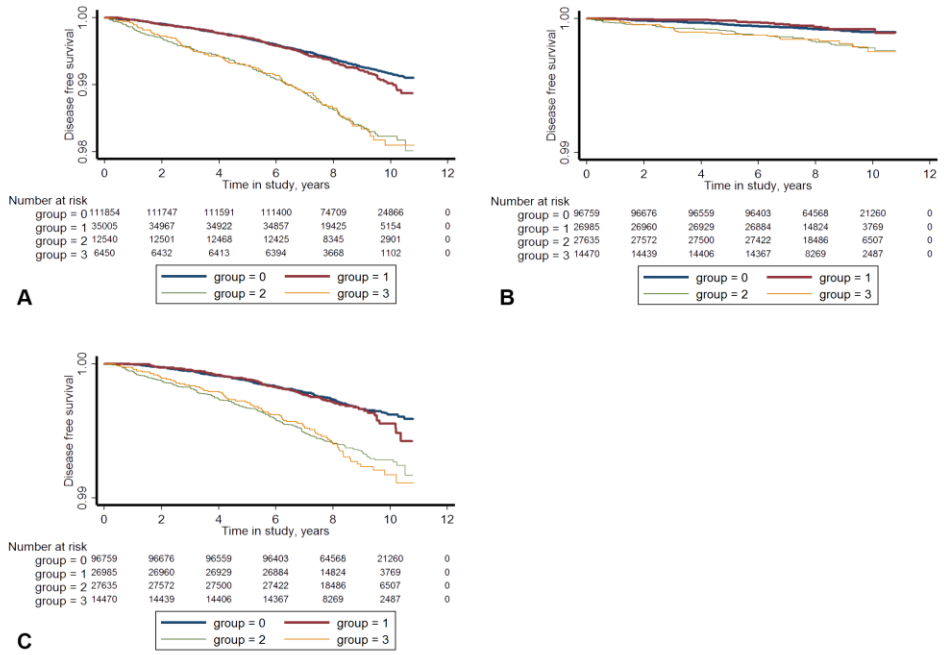

Figure 2