The Association Between Insulin Sensitivity Indices, ECG Findings and Mortality: A 40 Year Cohort Study

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The association between insulin sensitivity indices, ECG findings and mortality: a 40 year cohort study

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Abstract:

Background: Type 2 Diabetes is associated with insulin resistance and is a major risk factor for cardiovascular mortality. Insulin resistance can be evaluated non-invasively by insulin sensitivity indices, like the Mcauley index (MCAi), which is a function of fasting plasma insulin and triglycerides. We sought to further elucidate the association between insulin sensitivity indices and incidental ECG findings and all-cause and cardiovascular mortality in a large cohort followed for decades.

Methods: In a prospective study of the Israel cohort on Glucose Intolerance, Obesity and Hypertension (GOH) second phase (1979-1982) 1830 men and women were followed until December 2016 for cardiovascular mortality and December 2019 for all-cause mortality. ECGs were recorded and oral glucose tolerance tests performed during baseline. Insulin sensitivity indices were categorized into quartiles and evaluated against ECG findings and all-cause and cardiovascular mortality.

Results: Mean age at baseline was 52.0±8.1 years, and 75 (15.2%) and 47 (25.3%) participants in the upper quartiles (Q_{2-4}) and the lower quartile (Q_1) of the MCAi, presented with ischemic changes on ECG respectively (p=0.02). Multivariable analysis showed higher odds for ECG ischemic changes, for individuals in Q_1-MCAi (adjusted OR=1.7, 95%CI 1.02-2.8), compared with Q_{2-4}-MCAi, which attenuated when excluding individuals with diabetes (adjusted OR=1.6, 95%CI 0.9-2.7, p=0.09). Cox proportional-hazards regression showed an increased risk for all-cause mortality for individuals in Q_1-MCAi (HR=1.2, 95%CI 1.02-1.3) as well as an increased risk for cardiovascular mortality (HR=1.4, 95%CI 1.1-1.8) compared with Q_{2-4}-MCAi. Individuals in Q_4-Ln HOMA-IR and Q_1-QUICKI also presented with increased risk for all-cause-mortality (HR=1.2, 95%CI 1.04-1.4; and HR=1.2, 95%CI 1.04-1.4,

respectively). Other ISIs did not show significant association with cardiovascular mortality.

Conclusions: Higher insulin-resistance, according to the MCAi, associated with ECG changes, and with greater risk for all-cause and cardiovascular mortality over a 40-year follow-up. The MCAi may be considered as an early predictive and prognostic biomarker for CV-morbidity and mortality in adults.

Key words: Diabetes mellitus, Insulin sensitivity indices, ECG findings, All-cause mortality, cardiovascular mortality.

Introduction:

Type 2 diabetes mellitus is one of the most common chronic diseases of the modern world. According to the American diabetes association (1), the prevalence of diabetes in the general population in 2015 was 9.4% (30.3 million Americans) and 25.2% in the elderly population. In addition, 1.5 million new cases are reported every year (1,2).

Diabetes is a well-known risk factor for micro and macro-vascular complications (3-5) such as myocardial infarction, cerebral vascular accident, retinopathy and nephropathy. Recent studies have shown that even prediabetes was associated with vascular complications (5- 7). The underlying pathophysiological mechanisms of the disease are depleted pancreatic beta cell function and systemic insulin resistance (IR).

In order to evaluate pancreatic beta cells function and IR in a non-invasive manner, compared with the gold standard and intrusive euglycemic insulin clamp, a number of indices were developed and validated based on insulin and glucose blood levels (8-12). Commonly used indices include the Homeostatic model assessment (HOMA) (8, 9), the Matsuda Insulin Sensitivity Index (MISI) (10), the Quantitative Insulin Sensitivity Check Index (QUICKI) (11) and the Mcauley index (MCAi) (12). Selected insulin sensitivity indices description, normal values, formulas and classification are detailed in table 2.

The association between abnormal ECG findings and cardiovascular mortality and morbidity was previously described (14-15).

Previous studies have examined the association between metabolic syndrome and insulin sensitivity indices with ECG abnormalities, with inconclusive results (15-22). Bhatt et al. showed an association between log MISI and HOMA-derived measures with pathologic Q waves and left ventricular hypertrophy (LVH) on ECGs, on a homogeneous sample of 1,671 type 2 diabetic patients (22).

The association between abnormal values of insulin sensitivity indices and all cause and cardiovascular mortality is still not fully established and results are contradicting (23-24). De Boer et al (24) showed on a population of 3,138 older adults (age ≥65 years) without diabetes and after a 14.7-year median follow-up, an increased risk for all-cause mortality for individuals in the lower quartile of MISI (Hazard ratio 1.23 ,95%CI: 1.11-1.44). However after adjustment for eGFR the association was no longer statistically significant.

The discovery of innovative predictive and prognostic factors in the general population and specifically in patients with diabetes and those with prediabetes, beyond the conventional risk factors, is crucial in the prevention and reduction of cardiovascular morbidity and mortality.

We evaluated the association between insulin sensitivity indices and incidental ECG findings, and the association to all-cause and cardiovascular mortality over a 40-year follow-up.

Methods:

Study design and population:

The study is based on the cohort of the Israel Glucose Intolerance, Obesity and Hypertension (GOH) study (25). This is a prospective study, which began on 1967 and included 8400 Israeli Jews that were randomly sampled from the Israel population registry, according to sex, birth decade and ethnic origin (Yemenite, Asian, North Africans, and European-North Americans) stratification. During the second phase of the study (1979-1982), subjects underwent medical interviews, anthropometric measurements, extensive blood tests including glucose and insulin levels during

fasting and during a 2-hour oral glucose tolerance test (OGTT) and resting ECG recording, at regional medical centers.

Inclusion criteria for the present study were the presence of a resting ECG, as well as fasting glucose and fasting insulin plasma levels.

Out of 3,726 participants, primarily interviewed during the second phase, 2,469 underwent resting ECG recording, 2802 were tested for fasting glucose levels and 1843 were tested for fasting insulin levels.

Blood tests were evaluated using a single lab. Plasma glucose was determined with the automated Technicon Autoanalyser II (Technicon Instruments Corp, Tarrytown, NY) with the use of potassium ferricyanide reduction; plasma insulin level was determined in duplicate with the Phadebas Radioimmunoassay kit (Pharmacia Diagnostics Inc. Piscataway, NJ). The methodology of the GOH study was described extensively by Dankner et al (25).

Participants were followed until December 2019 for all-cause mortality and until December 2016 for cause specific mortality. Information on vital state was obtained from the National Population Registry and causes of death from the Israel Ministry of Health.

Cohort members agreed to participate in the study, and the study protocol was approved by the 1975 Declaration of Helsinki as reflected in a priori approval by the Sheba Medical Center's IRB.

ECG findings:

Twelve-lead ECG recordings were interpreted and encoded by a single cardiologist according to the Minnesota code classification system (26). ECG findings were

classified into subgroups using the Minnesota code manual 2009 and based on findings from a previous publication on the study population (27) into (table S-2): Arrhythmia, Right axis deviation, Left axis deviation, Atrioventricular conduction defect, Ventricular conduction defect, ST Junction (J) and segment depression, Miscellaneous findings, Nonspecific T wave changes, Nonspecific ST changes, Ischemic changes, Left Axis Deviation + Nonspecific T wave changes.

Insulin sensitivity indices (ISI):

Commonly used insulin sensitivity indices, examined in the current study, included the HOMA-Insulin resistance (IR) HOMA-IR, and the beta cell function HOMA-%B (8, 9), the MISI (10), the QUICKI (11) and the MCAi (12). Indices were calculated and analyzed according to quartiles as follow:

1. HOMA-IR and HOMA-%B are usually not normally distributed, as observed in the current study. Consequently, HOMA-IR and HOMA-%B were logarithmically transformed implementing natural log (Ln) on the equation.

HOMA was calculated as follow (8, 9):

$$\mathrm{HOMA-IR} = \mathrm{FPI} \times \frac{\mathrm{FPG}}{405}$$

$$\mathrm{HOMA-\%B} = 360 \times \frac{\mathrm{FPI}}{(\mathrm{FPG} - 63)}$$

Were FPI refer to fasting insulin levels in$\left[\frac{\mathrm{mU}}{\mathrm{L}}\right]$.

FPG refer to fasting glucose levels in$[\frac{\mathrm{mg}}{\mathrm{dl}}]$.

2. MISI mean glucose plasma levels were calculated using: fasting glucose, 60 and 120 minutes glucose after an oral administration of 100gr glucose. Mean insulin plasma levels were calculated using fasting insulin and insulin levels at 30, 60 and 120 minutes after the oral administration of 100gr glucose. As with HOMA, MISI was logarithmically transformed implementing natural log (Ln) on the equation. MISI was calculated as follow (10):

$$\text{MISI} = \frac{10{,}000}{\sqrt{(\text{FPG} \times \text{FPI}) \times \ [\text{mean glucose during OGTT x mean insulin during OGTT}]}}$$

3. QUICKI was normally distributed and calculated as follow (11):

$$\text{QUICKI} = \frac{1}{\text{Log FPI} + \text{Log FPG}}$$

4. MCAi was normally distributed and calculated as follow (12):

$$\text{MCAi} = e^{[2.63 - 0.28 * Ln\ \text{FPI} - 0.31 * Ln\ trig]}$$

Were FPI refer to fasting insulin levels in $\left[\frac{\text{mU}}{\text{L}}\right]$.

Trig refer to fasting triglycerides levels in $\left[\frac{\text{mMole}}{\text{L}}\right]$.

Endpoints:

The primary outcome was 40-year all-cause mortality. The secondary outcome was cardiovascular mortality. Individual follow-up time was calculated starting at the examination date (physical examination and blood tests) during the second phase and

until time of death or end of follow up- earliest of these. Primary cause of death was reported using International Classification of Diseases (ICD) 9 or ICD 10.

The Sheba Medical Center Review Board provided approval for this study (approval number 1180). All patients gave their verbal consent to participate in the study during baseline data collection.

Statistical methods

In-group differences between ECG findings were evaluated using the Chi square test or the Fisher's exact test for small cells and the Student t test for normally distributed variables or the Mann-Whitney test for nonparametric variables, with the two-sided p-values (p) set at the 0.05 level of significance. The association between insulin sensitivity indices and ECG findings was evaluated using a multivariable logistic regression model and presented by Odd Ratios with 95% confidence interval (95%CI) adjusted for age, sex, ethnicity, smoking status, BMI, blood pressure, cholesterol and glycemic state.

The associations between insulin sensitivity indices and 40-year all cause and CVD mortality were evaluated using Cox proportional hazards models adjusted for the same covariates as mentioned above. ISI were tested in a separate model each. Proportional hazards assumptions were tested in the models by entering into the model an interaction term between time-to-event for each covariate and by log minus log plot. A test for multi-collinearity was performed using Spearman's rank correlation coefficient for model covariates. Covariates with a correlation above 60% were not included in the same model. Kaplan Meier survival curves for ECG findings and insulin sensitivity indices were compared using log-rank test. Statistical analysis was performed using SPSS version 23.0.

166 **Results:**

167 Baseline characteristics (table 1):

168 The final cohort comprised of 1830 subjects who met the inclusion criteria, of whom
169 915 (50%) examinees had ECG findings that were classified as abnormal. Mean age
170 of individuals with abnormal ECG was 53.7±7.9 years whereas that of individuals
171 with normal ECG was 50.3 ±7.8 years (P<0.001), with a greater male proportion in
172 the abnormal vs the normal ECG group, 53.1 and 49.2% respectively, p=0.09. Blood
173 pressure, BMI, total cholesterol, fasting triglycerides, fasting glucose and fasting
174 insulin, as well as diabetes were significantly higher in the abnormal ECG group. No
175 differences were observed between the two ECG groups regarding ethnic origin and
176 smoking status. When categorized, all 5 ISIs indicated a greater insulin resistance in
177 the ECG abnormal group. In MISI, 28.8% and 21.2% individuals belonged to the Q1
178 in the abnormal and the normal ECG groups, respectively, p=0.004. The respective
179 proportions for the MCAi were 26.9% and 23.1%, p=0.06.

180 ECG findings:

181 Ischemic changes, defined as Q and QS abnormal patterns or ST segment elevation,
182 were observed in 128 (7%) participants (Table S-2).

183 All ISIs were significantly associated with "any ECG" abnormality, although after
184 adjustment for age, sex, origin, BMI, blood pressure, cholesterol, smoking and
185 glycemic state, none of the ISI remained statistically significant. Ischemic changes on
186 ECG were associated with greater adjusted odds for the MCAi Q_1 compared to MCAi
187 $Q_{2\text{-}4}$ (OR=1.7, 95%CI: 1.02-2.8, P=0.04) (Figure 1, Table S-3). Male sex, older age
188 and higher blood pressure were also associated with increased risk for ischemic
189 changes on ECG (not shown). The association of the MCAi with the various ECG

abnormalities are presented in Figure 1, showing an overall odd for any ECG abnormality of 1.10 (95%CI: 0.80-1.40).

In the diabetes group, a large proportion of individuals (47%-64%) belonged to the abnormal quartiles of the ISIs as expected. In the prediabetes group, about 27-30% were categorized in the abnormal ISIs (Table S-4a).

No statistically significant associations between the other ISIs and ECG findings were observed in the adjusted multivariable analyses (Table S-3). A sensitivity analysis excluding diabetic individuals from the models is presented in Table S-4b, showing borderline association between the MACi and ischemic changes (adjusted OR=1.6, 95%CI 0.9-2.7, p=0.09) for Q_1 vs Q_{2-4}.

<u>All-cause and cause specific mortality:</u>

Participants were followed until December 2019 for all-cause mortality and until December 2016 for cardiovascular mortality. Median follow up was 31 years and 1,276 (69.7%) of all participants died during that period. Median follow up for cardiovascular mortality was 37 years and 377 (20.6%) participants died from cardiovascular causes. Table S-1 is presenting the baseline characteristics of the study cohort according to vital status and cause of death. As expected, those who died from all cause and from cardiovascular mortality were older than those who remained alive by the end of the follow-up. Those who died were of male predominance, had a higher proportion of diabetes, were more hypertensive, and obese. Mean fasting glucose values were in the prediabetic range in those who died from all-cause and from cardiovascular causes compared to those remaining alive (109±34 and 115±43 vs. 97±14 mg/dl, respectively), and their total cholesterol was higher as well (224±55 and

232±57 vs 214±52mg/dl, respectively). Insulin resistance was more pronounced in those who died than those remaining alive, as evident by all 5 IRIs.

Kaplan-Meier survival curves (figure 2A) and log-rank test demonstrated a statistically significant shorter time until death for the abnormal ECG group ($P<0.001$), and for those in the abnormal quartile (Q_1) of the MACi $P<0.001$ (Figure 2B). This was also observed for the other insulin sensitivity indices. Kaplan-Meier survival curves (Figure 2C) and log-rank test for cardiovascular mortality demonstrated a statistically significant shorter time until death for individuals in the MCAi lower quartile (Q_1) $P<0.001$.

Median survival times of individuals in the lower quartile (Q_1) of MCAi was 28 years (95%CI, 26.6–29.4) and 33 years (95%CI: 31.9–34.1) in the upper MCAi quartiles (Q_{2-4}), Log-rank test: $p < 0.001$. Table 3 presents the results of the univariate and multivariate Cox regression analyses. Adjusting for age, sex, origin, BMI, blood pressure, cholesterol, smoking and glycemic state. Individuals in the lower quartile of MCAi showed a 20% greater all-cause mortality risk compared with the upper quartiles (95%CI: 1.02-1.3, P=0.02). An increased risk for all-cause mortality was also observed in Q_4-Ln HOMA-IR and Q_1-QUICKI as well, HR=1.2 (95%CI, 1.04-1.4, P=0.01) and HR=1.2 (95%CI, 1.04-1.4, P=0.01) respectively. Male sex, smoking status, diabetes morbidity, abnormal blood pressure, and obesity, were all found to significantly associate with all-cause mortality.

After adjusting for age, sex, origin, BMI, blood pressure, total cholesterol, smoking and glycemic state, a greater risk for cardiovascular mortality was observed for individuals in the lower quartile of MCAi, compared with upper quartiles (HR=1.4,

95%CI: 1.1-1.8, p=0.007). The remaining indices did not demonstrate a significant risk for cardiovascular mortality (Table 3).

Insulin resistance, expressed by the MACi-Q_1 significantly associated with all-cause mortality (adjusted HR=1.2, 95%CI 1.1, 1.4) and with a borderline significance for cardiovascular mortality (adjusted HR=1.3, 95% CI 0.99, 1.7) in the non-diabetic cohort members (Table S-4c).

Discussion

The current study, performed on ethnically heterogeneous cohort of men and women, has shown a significant association between insulin resistance (IR), reflected by the MACi and ischemic changes on ECG (Q-QS abnormality, ST elevation). Persistence of the association between the MACi and ischemic changes on ECG, when excluding individuals with diabetes from the multivariable model, emphasize the association between IR and cardiovascular morbidity.

These findings are in line with other studies on insulin sensitivity indices, particularly abnormal MACi values, and increased risk for CHD (22, 24, 29). Effoe et al (29) followed 3,565 black men and women, free of diabetes mellitus and cardiovascular disease at baseline, for CAD incidence, over a median follow-up of 8.4 years (29). They showed a decreased risk for CAD with each SD increase in the MCAi (HR=0.80; 95% CI: 0.67–0.96). Moreover, MACi and HOMA-IR were associated with CAD (HR=0.71, 95% CI: 0.55–0.92 and HR=1.33, 95% CI: 1.03–1.72, respectively), but not with stroke risk.

To point out, Q and QS Patterns and ST segment elevation are primarily associated with CAD (30-31). However, other etiologies should be considered, such as left

ventricular hypertrophy, effect of medications (e.g. digitalis), or infiltrative diseases such as cardiac amyloidosis.

Sex, age, hypertension and obesity in the current study were also associated with an increased risk for the occurrence of ischemic changes, as expected, as they are all well-known cardiovascular risk factors.

Our findings demonstrate an additional risk of 20% for all-cause mortality and 40% for cardiovascular mortality in cohort members of the MCAi lower quartile compared with upper quartiles, independently of the presence of diabetes. Furthermore, the abnormal quartiles of Ln HOMA-IR and QUICKI were also associated with an additional 20% risk for all-cause mortality and for cardiovascular mortality, but reached statistical significance for all-cause mortality only.

All-cause mortality was mainly attributed to cardiovascular mortality (20.6%) as the primary cause of death in the cohort. The secondary cause of death was malignancy associated mortality (15.8%). In addition to the MCAi, male sex, age, origin (Middle Eastern), obesity, high blood pressure and diabetes, were also associated with a higher risk for cardiovascular mortality.

MCAi was the only ISI that showed a significant association with ischemic changes on ECG in addition to increased risk for all cause and cardiovascular mortality. Moreover, a significant association between MCAi lower quartile and all-cause mortality was observed even after excluding diabetic subjects from the cohort (as detailed below). This may be attributed to the inclusion of fasting triglycerides in the MCAi calculation. Fasting triglycerides reflects abnormal lipids metabolism as a direct and early outcome of insulin resistance (32-33) and perhaps increases the risk for coronary artery disease (CAD) and cardiovascular mortality (33-34). The direct

association between increased triglycerides and cardiovascular morbidity and mortality remain controversial. However several meta-analyses described an increased risk for CAD for individuals with abnormal triglycerides levels (33-34). A meta-analysis (34) from 2 prospective cohort studies on 44,237 Western middle-aged men and women, the Reykjavik study and the European Prospective Investigation of Cancer (EPIC)-Norfolk study, showed an increased risk for CHD after adjustment for cardiovascular risk factors (HR=1.43, 95% CI: 1.23 –1.65, and HR=1.52, 95%CI: 1.24 - 1.89 for individuals in the top third of log-triglyceride in the Reykjavik and the Norfolk studies, respectively). Adjustment for cardiovascular risk factors substantially attenuated the above observed associations supporting the hypothesis that increased triglycerides reflect metabolic abnormalities such as diabetes and obesity that increases CVD incidence rather than a direct contribution (35). Moreover, increased triglycerides further contribute to beta-cell dysfunction by a direct toxicity mechanism and enhances the insulin resistance state and therefore increases the risk for cardiovascular morbidity and mortality (32).

In line with other studies (22,36), the present study further supports the use of MCAi as an accurate and early detection methods for insulin resistance compared with other ISI. Kim, T. J et al (36) demonstrated that MCAi had the strongest correlation with insulin resistance, the highest area under the curve, specificity, positive predictive value and negative predictive value to distinguish individuals with metabolic syndrome from healthy subjects.

The study population mainly consisted of non-diabetic subjects and only 218 (11.9%) participants were diagnosed with diabetes at baseline. A sensitivity analysis excluding examinees with the diagnosis of diabetes, comprised of n=1612 non diabetic individuals, and did not reveal a statistically significant association between ISIs and

ECG findings. However, an increased risk for all-cause and cardiovascular mortality was observed (HR=1.2, 95%CI: 1.1-1.4, and HR=1.3, 95%CI: 0.99-1.7, respectively) for individuals in the MCAi lower quartile (Q_1) compared to upper quartiles (Q_{2-4}). This finding underscores the importance of the MCAi as a potentially sensitive biomarker for metabolic abnormality which calls for further evaluation.

Strengths and limitations

Our findings should be interpreted under the following limitation: The oral glucose tolerance test (OGTT), was carried out using 100 gr of glucose ingestion instead of 75 gr as recommended by the American Diabetes Association (1), since at the time of the examination (prior to the recommendations, 1979–1982) no clear guidelines were present for this test. In addition, the use of 100gr of glucose instead of 75 gr, was reported to enhance the insulin response and insulin secretion (38), and to have a minimal effect on the glucose level and OGTT results (39).

Another limitation is the oversampling of Yemenites in the GOH cohort, which was done in order to provide statistical power to study this minority in relation to hypertension and diabetes incidence. While this may reduce the external validity of the study, the multivariable analysis was adjusted for ethnicity.

In the current study, MISI mean glucose plasma levels was calculated using 0,60 and 120 minutes after OGTT and mean insulin plasma levels using 0,30,60 and 120 minutes after OGTT. However, the use of fewer measurements for the mean insulin and glucose calculation is acceptable in the literature (10-11, 40). In addition, only participants with the presence of every insulin and glucose measurement after OGTT were included for MISI calculation (n=1071). A sensitivity analysis was performed

including participants with existing data from every glucose and insulin measurements available (n=1830) for the calculation of MISI with similar findings.

Despite these limitations, the study presents a number of key advantages: this is a cohort study with both men and women, representing the diverse population of the Israeli- Jewish population, with a prolonged follow up time of 40 years. Furthermore, all ECGs were interpreted by a single cardiologist, avoiding inter-observer variability, and blood tests were performed for research purposes only by a single lab which conformed to the highest standards.

Conclusion:

Our findings demonstrate an association between higher insulin resistance, presented by the lower quartile of the MCAi, and ischemic changes on ECG. MCAi lower quartile was associated with higher risk for approximately 40-year all-cause and cardiovascular mortality in an adult population, and may be consider as a simple and readily available biomarker for early cardiovascular signs and for greater mortality risk.

List of abbreviations:

HOMA-IR, Homeostatic model assessment -Insulin resistance; HOMA-%B - Homeostatic model assessment – percent beta cell function; MISI, Matsuda Insulin Sensitivity Index; QUICKI, Quantitative Insulin Sensitivity Check Index; MCAi, Mcauley index.

ISI, insulin sensitivity indices.

OGTT, oral glucose tolerance test.

Declarations:

Ethics approval and consent to participate: The Sheba Medical Center Review Board provided approval for this study (approval number 1180). All patients gave their verbal consent to participate in the study during baseline data collection.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author upon request.

Competing interests: The authors declare that they have no competing interests.

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Author contributions: YM contributed to the design of the study and conducting the data analysis, the interpretation of data and drafting of the manuscript. RD and AC contributed to the acquisition of the data, to the conception and design of the work, to the data analysis and drafting of the manuscript. DR contributed to the conception and design of the work. DR, AC and RD critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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References:

1. Centers for Disease Control and Prevention. National diabetes statistics report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services. 2020.
2. Classification and diagnosis of diabetes. *Diabetes Care* 2016; 39 Suppl 1:S13–22.
3. Selvin E. Meta-Analysis: Glycosylated Hemoglobin and Cardiovascular Disease in Diabetes Mellitus. *Ann Intern Med* 2004; 21;141(6):421.
4. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979; 11;241(19):2035–2038.
5. Fowler MJ. Microvascular and macrovascular complications of diabetes. *Clinical Diabetes* 2008; 1;26(2):77–82.
6. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *J Am Coll Cardiol* 2010; 30: 55(13):1310–1317.
7. Plantinga LC, Crews DC, Coresh J, et al. Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. *Clin J Am Soc Nephrol* 2010; 5(4):673–682.
8. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004; 27(6):1487–1495.
9. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28(7):412–419.
10. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 1999; 22(9):1462–1470.
11. Katz A, Sridhar SN, Kieren M. Quantitative Insulin Sensitivity Check Index: A Simple, Accurate Method for Assessing Insulin Sensitivity in Humans. *The Journal of Clinical Endocrinology & Metabolism* 2000 April; Vol. 85, No. 7.

12. McAuley KA, Williams SM, Mann JI, Walker RJ, Lewis-Barned NJ, Temple LA, Duncan AW. Diagnosing insulin resistance in the general population. *Diabetes Care* 2001 Mar;24(3):460-4.
13. Turner RC, Holman RR, Matthews D, Hockaday TD, Peto J. Insulin deficiency and insulin resistance interaction in diabetes: estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. *Metabolism* 1979; 28:1086–1096.
14. Kannel WB, Anderson K, McGee DL, Degatano LS, Stampfer MJ. Nonspecific electrocardiographic abnormality as a predictor of coronary heart disease: the Framingham Study. *Am Heart J*. 1987 Feb;113(2 Pt 1):370–376.
15. Rose G, Baxter PJ, Reid DD, McCartney P. Prevalence and prognosis of electrocardiographic findings in middle-aged men. *Heart*. 1978 Jun 1; 40(6):636–643.
16. Granér M, Pentikäinen MO, Siren R, Nyman K, Lundbom J, Hakkarainen A, et al. Electrocardiographic changes associated with insulin resistance. *Nutr Metab Cardiovasc Dis*. 2014 Mar; 24(3):315–320.
17. Lind L, Sundström J, Lithell H. Cardiovascular risk factors and electrographical characteristics and abnormalities in middle-aged males. *J Intern Med*. 1997 Feb; 241(2):109–113.
18. Kim HK, Kim CH, Ko KH, Park SW, Park JY, Lee KU. Variable association between components of the metabolic syndrome and electrocardiographic abnormalities in Korean adults. *Korean J Intern Med*. 2010 Jun 1; 25 (2):174–180.
19. Stamler R, Stamler J, Schoenberger JA, Shekelle RB, Collette P, Shekelle S, et al. Relationship of glucose tolerance to prevalence of ECG abnormalities and to 5-year mortality from cardiovascular disease: findings of the Chicago Heart Association Detection Project in Industry. *J Chronic Dis*. 1979; 32(11-12):817–828.
20. Dinh W, Lankisch M, Nickl W, Scheyer D, Scheffold T, Kramer F, et al. Insulin resistance and glycemic abnormalities are associated with deterioration of left ventricular diastolic function: a cross-sectional study. *Cardiovasc Diabetol*. 2010 Oct 15; 9:63.

21. Marita AR, Desai A, Mokal R, Agarkar RY, Dalal KP. Association of insulin resistance to electrocardiographic changes in non-obese Asian Indian subjects with hypertension. *Endocr Res*. 1998 May; 24 (2):215–233.

22. Bhatt AB, Mulvey CK, Qasim AN, Nair JV, Rickels MR, Prenner SB, et al. Selective association of electrocardiographic abnormalities with insulin sensitivity and beta-cell function in type 2 diabetes mellitus: a cross-sectional analysis. *Diabetes Metab Res Rev*. 2016 Apr 21;32(7):736–744.

23. Barr E, Cameron A, Balkau B, Zimmet P, Welborn T, Tonkin A, Shaw J. HOMA insulin sensitivity index and the risk of all-cause mortality and cardiovascular disease events in the general population: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) study. *Diabetologia* 2010, 53(1), 79-88.

24. De Boer IH, Katz R, Chonchol MB, Fried LF, Ix JH, Kestenbaum B, Siscovick DS. Insulin resistance, cystatin C, and mortality among older adults. *Diabetes Care* 2012; 35(6): 1355-1360.

25. Dankner R, Olmer L, Kaplan G, Chetrit A. The joint association of self-rated health and diabetes status on 14-year mortality in elderly men and women. *Qual Life Res*. 2016 May 2; 25(11):2889–2896.

26. Prineas RJ, Crow RS, Zhang ZM. The Minnesota code manual of electrocardiographic. London: Springer London; 2010.

27. Goldman A, Hod H, Chetrit A, Dankner R. Incidental abnormal ECG findings and long-term cardiovascular morbidity and all-cause mortality: A population based prospective study. *Int J Cardiol*. 2019 Nov 15;295:36–41.

28. Laws A, Reaven GM. Evidence for an independent relationship between insulin resistance and fasting plasma HDL-cholesterol, triglyceride and insulin concentrations. *J Intern Med*. 1992 Jan; 231(1):25–30.

29. Effoe VS, Wagenknecht LE, Echouffo Tcheugui JB, Chen H, Joseph JJ, Kalyani RR, et al. Sex differences in the association between insulin resistance and incident coronary heart disease and stroke among blacks without diabetes mellitus: the Jackson heart study. *J Am Heart Assoc*. 2017 Feb 2; 6(2).

30. de Bliek EC. ST elevation: Differential diagnosis and caveats. A comprehensive review to help distinguish ST elevation myocardial infarction from nonischemic etiologies of ST elevation. *Turk J Emerg Med*. 2018 Mar;18(1):1–10.

31. Deanfield JE, Shea M, Ribiero P, de Landsheere CM, Wilson RA, Horlock P, et al. Transient ST-segment depression as a marker of myocardial ischemia during daily life. *Am J Cardiol*. 1984 Dec 1;54(10):1195–1200.

32. Miller JP. Serum triglycerides, the liver and the pancreas. *Curr Opin Lipidol*. 2000 Aug;11(4):377–382.

33. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S. (2006). Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation*. 2007 Jan 30 [cited 2019 Feb]; 115 (4): 450–8.

34. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3:213–219.

35. Navar AM. The evolving story of triglycerides and coronary heart disease risk. *JAMA*. 2019. Jan 29;321(4):347–349.

36. Kim TJ, Kim HJ, Kim YB, Lee JY, Lee HS, Hong JH, et al. Comparison of surrogate markers as measures of uncomplicated insulin resistance in korean adults. *Korean J Fam Med*. 2016 May 26;37(3):188–196.

37. Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, Carmena R. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. *Diabetes Care* 2003;26:3320–3325.

38. Cerasi E, Ependić S, Luft R. Dose-response relation between plasma-insulin and blood-glucose levels during oral glucose loads in prediabetic and diabetic subjects. *Lancet* 1973 Apr 14;1(7807):794–797.

39. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. *Diabetes* 1979 Dec; 28(12):1039–1057.

40. DeFronzo RA, Matsuda M. Reduced time points to calculate the composite index. *Diabetes care* 2010 Jul;33(7):e93.

Figure legends:

Figure 1: Odds Ratios for the association between higher insulin resistance, according to the Mcauley index (MCAi) lower quartile (Q_1) compared with upper quartiles (Q_{2-4}), and ECG findings. Multivariable [a] logistic regression analysis.

[a] Adjusted for: Age, Sex, Origin, BMI category, Smoking category, Blood Pressure category, Glycemic state, Total Cholesterol category.

BMI categories: Normal < 25 kg/m^2, Overweight, 25 – 29.9 kg/m^2, Obese, BMI ≥ 30 kg/m^2; Smoking categories: current or past smoker vs never smoked; Blood pressure category: Normal- systolic BP < 140 mmHg and diastolic BP < 90mmHg, Intermediate - systolic BP ≥ 140 mmHg or diastolic BP ≥90 mmHg, Hypertension systolic BP ≥ 140 mmHg and diastolic BP ≥ 90 mmHg; Glycemic state: normoglycemia, prediabetes, diabetes; Total cholesterol categories: Normal < 200 mg/dl, Borderline-high 200–239 mg/dl, High ≥ 240 mg/dl.

Fig. 2. Kaplan-Meier survival curves for (A) any ECG abnormality and all-cause mortality; (B) Insulin resistance according to the Mcauley index (MCAi) Q_1 vs Q_{2-4} and all-cause mortality; and (C) Insulin resistance according to the Mcauley index (MCAi) Q_1 vs Q_{2-4} and cardiovascular mortality.

Median survival in the normal ECG group was 35 years (95%CI, 33.8–36.2) and 27 years (95%CI, 25.8–28.2) in the abnormal ECG group. Median survival in the lower MCAi quartile (Q_1) was 28 (95%CI, 26.6–29.4) years and 33 (95%CI, 31.9–34.1) years in the upper MCAi quartiles (Q_{2-4}). Mean survival for cardiovascular mortality in the lower MCAi quartile (Q_1)

was 30.3 years (95%CI, 28.8–31.9) and 34.1 years (95%CI, 33.3–34.8) in the upper MCAi quartiles ($Q_{2\text{-}4}$).

Figures

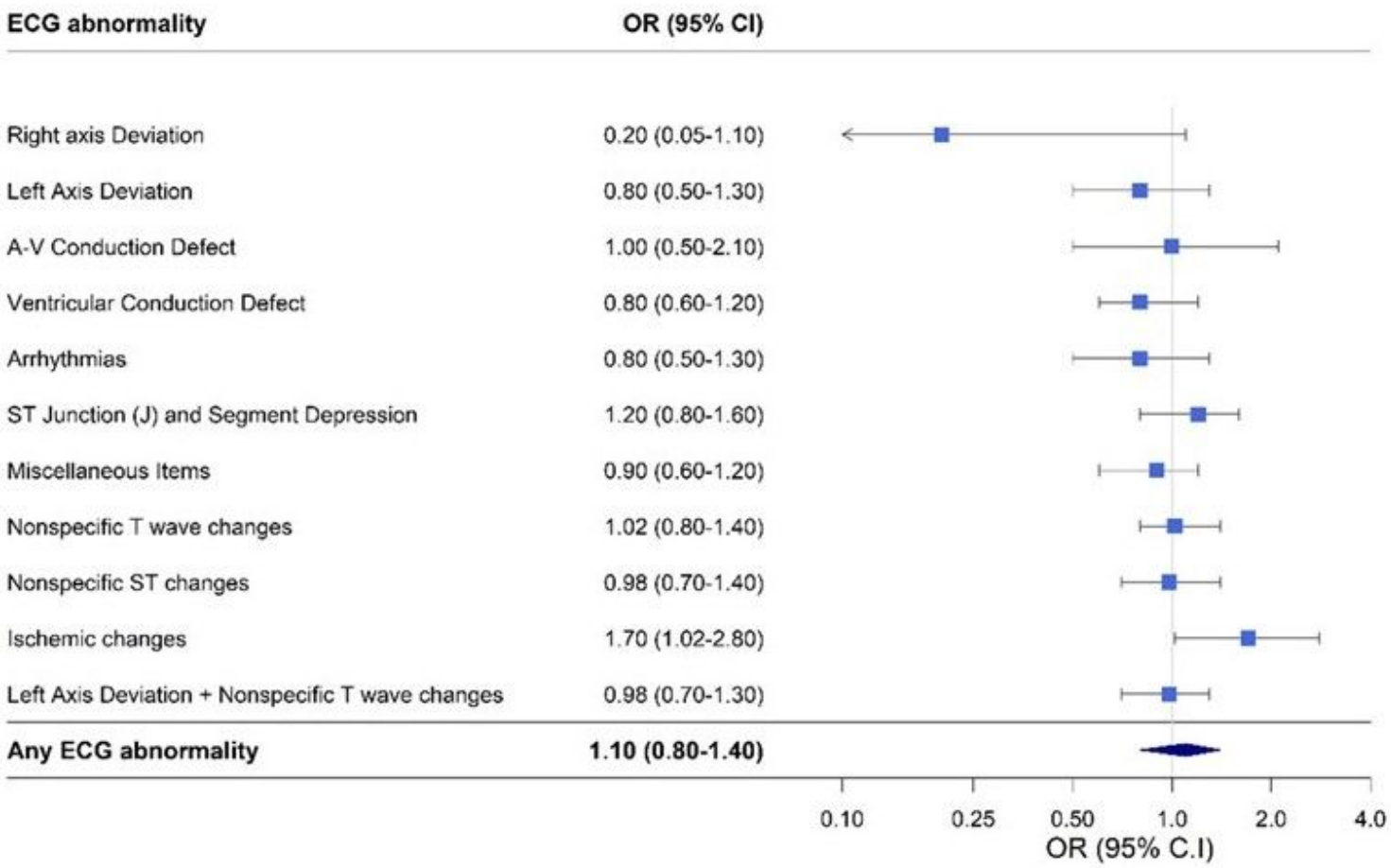

Figure 1

Odds Ratios for the association between higher insulin resistance, according to the Mcauley index (MCAi) lower quartile (Q1) compared with upper quartiles (Q2-4), and ECG findings. Multivariable a logistic regression analysis. a Adjusted for: Age, Sex, Origin, BMI category, Smoking category, Blood Pressure category, Glycemic state, Total Cholesterol category. BMI categories: Normal < 25 kg/m2, Overweight, 25 – 29.9 kg/m2, Obese, BMI ≥ 30 kg/m2; Smoking categories: current or past smoker vs never smoked; Blood pressure category: Normal- systolic BP < 140 mmHg and diastolic BP < 90mmHg, Intermediate - systolic BP ≥ 140 mmHg or diastolic BP ≥90 mmHg, Hypertension systolic BP ≥ 140 mmHg and diastolic BP ≥ 90 mmHg; Glycemic state: normoglycemia, prediabetes, diabetes; Total cholesterol categories: Normal < 200 mg/dl, Borderline-high 200–239 mg/dl, High ≥ 240 mg/dl.

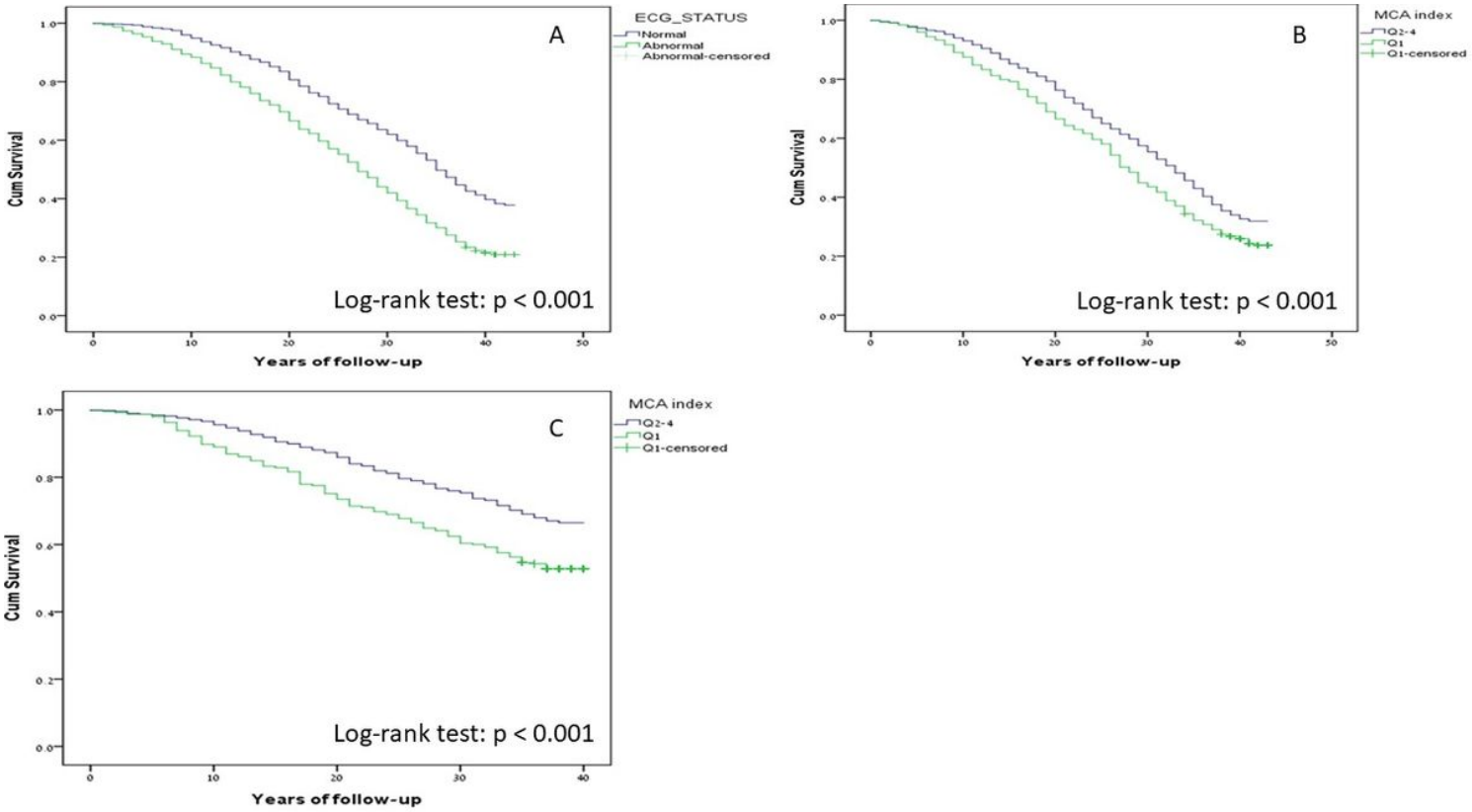

Figure 2

Kaplan-Meier survival curves for (A) any ECG abnormality and all-cause mortality; (B) Insulin resistance according to the Mcauley index (MCAi) Q1 vs Q2-4 and all-cause mortality; and (C) Insulin resistance according to the Mcauley index (MCAi) Q1 vs Q2-4 and cardiovascular mortality. Median survival in the normal ECG group was 35 years (95%CI, 33.8–36.2) and 27 years (95%CI, 25.8–28.2) in the abnormal ECG group. Median survival in the lower MCAi quartile (Q1) was 28 (95%CI, 26.6–29.4) years and 33 (95%CI, 31.9–34.1) years in the upper MCAi quartiles (Q2-4). Mean survival for cardiovascular mortality in the lower MCAi quartile (Q1) was 30.3 years (95%CI, 28.8–31.9) and 34.1 years (95%CI, 33.3–34.8) in the upper MCAi quartiles (Q2-4).

Supplementary Files

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