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Association between varying cut-points of intermediate hyperglycemia and risk of mortality, cardiovascular events and chronic kidney disease: a systematic review and meta-analysis

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ABSTRACT

Introduction We conducted a systematic review and meta-analysis to evaluate the updated evidence regarding prediabetes for predicting mortality, macrovascular and microvascular outcomes.

Research design and methods We identified English language studies from MEDLINE, PubMed, OVID and Cochrane database indexed from inception to January 31, 2020. Paired reviewers independently identified 106 prospective studies, comprising nearly 1.85 million people, from 27 countries. Primary outcomes were all-cause mortality (ACM), cardiovascular mortality (CVDM), cardiovascular disease (CVD), coronary heart disease (CHD) and stroke. Secondary outcomes were heart failure, chronic kidney disease (CKD) and retinopathy.

Results Impaired glucose tolerance was associated with ACM; HR 1.19, 95% CI (1.15 to 1.24), CVDM; HR 1.21, 95% CI (1.10 to 1.32), CVD; HR 1.18, 95% CI (1.11 to 1.26), CHD; HR; 1.13, 95% CI (1.05 to 1.21) and stroke; HR 1.24, 95% CI (1.06 to 1.45). Impaired fasting glucose (IFG) 110–125 mg/dL was associated with ACM; HR 1.17, 95% CI (1.13 to 1.22), CVDM; HR 1.20, 95% CI (1.09 to 1.33), CVD; HR 1.21, 95% CI (1.09 to 1.33), CHD; HR; 1.14, 95% CI (1.06 to 1.22) and stroke; HR 1.22, 95% CI (1.07 to 1.40). IFG 100–125 mg/dL was associated with ACM; HR 1.11, 95% CI (1.04 to 1.19), CVDM; HR 1.14, 95% CI (1.03 to 1.25), CVD; HR 1.15, 95% CI (1.05 to 1.25), CHD HR; 1.10, 95% CI (1.02 to 1.19) and CKD; HR; 1.09, 95% CI (1.01 to 1.18). Glycosylated hemoglobin A1c (HbA1c) 6.0%–6.4% was associated with ACM; HR 1.30, 95% CI (1.03 to 1.66), CVD; HR 1.32, 95% CI (1.00 to 1.73) and CKD; HR 1.50, 95% CI (1.32 to 1.70). HbA1c 5.7%–6.4% was associated with CVD HR 1.15, 95% CI (1.02 to 1.30), CHD; HR 1.28, 95% CI (1.13 to 1.46), stroke; HR 1.23, 95% CI (1.04 to 1.46) and CKD; HR 1.32, 95% CI (1.16 to 1.50).

Conclusion Prediabetes is an elevated risk state for macrovascular and microvascular outcomes. The prevention and management of prediabetes should be considered.

Significance of this study

What is already known about this subject?

- WHO and the American Diabetes Associaiton (ADA) differ on the definitions of the lower thresholds of impaired fasting glucose and prediabetic glycosylated hemoglobin A1c (HbA1c).
- Prediabetes is associated with increased risk for type 2 diabetes.
- There is evidence to indicate that impaired glucose tolerance and impaired fasting glucose are also associated with adverse mortality and cardiovascular outcomes.

What are the new findings?

- Impaired glucose tolerance, impaired fasting glucose and elevated HbA1c are associated with and increased risk of mortality, cardiovascular outcomes and chroic kidney disease.
- Elevated HbA1c is associated with an icreased risk of both macrovascular and microvascular outcomes.
- The lower cut-point of intermediate HbA1c was associated with increased cardiovascular events while the higher cut-point was associated with increased mortality.
- Both HbA1c cut-points as well as impaired fasting glucose ADA were associated with increased risk of incident chronic kidney disease.

How might these results change the focus of research or clinical practice?

- Prediabetes is an elevated risk state for adverse events beyond type 2 diabetes, and the prevention and management of prediabetes including elevated HbA1c should be considered.

INTRODUCTION

Elevated blood glucose concentrations, such as impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and elevated glycosylated hemoglobin A1c (HbA1c), represent stages of glycemia considered too high to be in the normal range, but below the threshold of what is considered type 2 diabetes.[1] While elevated glucose poses an increased risk for

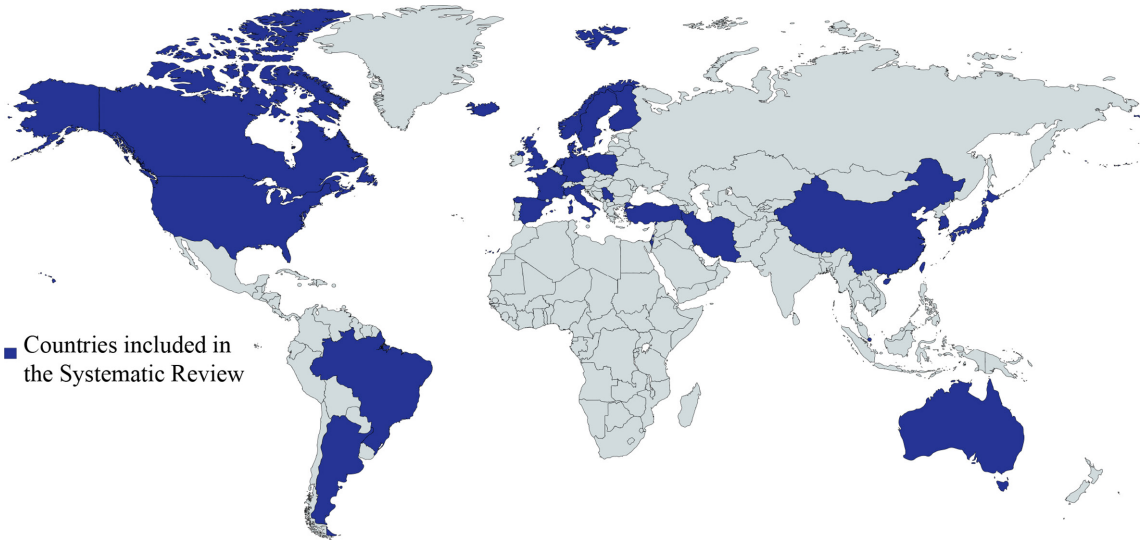

Figure 1 Countries included in the systematic review. Number of cohorts including each country: Argentina: 1; Australia: 3; Brazil: 1; Canada: 1; China: 10; Denmark: 3; Fiji: 1; Finland: 7; France: 1; Germany: 4; Iceland: 2; Iran: 2; Israel: 2; Italy: 3; Japan: 10; Mauritius: 2; The Netherlands: 4; Norway: 2; Poland: 1; Serbia: 1; Singapore: 2; South Korea: 6; Spain: 1; Sweden: 2; Turkey: 1; UK: 8; USA: 23.

type 2 diabetes, individuals in this intermediate range may also be at increased risk for all-cause mortality, cardiovascular mortality, incident cardiovascular events and microvascular complications. Importantly, the American Diabetes Association (ADA) and WHO currently differ on how they define the lower threshold for IFG as well as identifying an intermediate stage of HbA1c. While WHO defines IFG as fasting glycemia between 110 and 125 mg/dL,[2] the ADA has reduced the lower threshold to 100 mg/dL.[1] Furthermore, WHO does not recommend HbA1c as a suitable test for the diagnosis of intermediate glycemia.[3] However, the ADA suggests a cut-point of HbA1c 5.7%–6.4% for intermediate hyperglycemia, while an International Expert Committee (IEC)[4] as well as the UK-based National Institute for Health and Clinical Excellence[5] both recommend using HbA1c 6.0%–6.4%.

In addition, IFG, IGT and elevated HbA1c represent different types of hyperglycemia, possibly varying in pathophysiological mechanisms.[6 7] For example, insulin resistance may be the primary defect in individuals with isolated IGT, while dysfunction in insulin secretion has been seen as the earliest observed defect in individuals with IFG.[6 7] It is important to investigate if the varying forms of intermediate hyperglycemia predict a different risk spectrum for developing mortality, cardiovascular disease (CVD) or microvascular complications. We, therefore, conducted a systematic review and meta-analysis of 106 prospective studies, comprising nearly 1.85 million people, from 27 countries (figure 1), to evaluate the non-diabetic cut-points of fasting glucose, 2-hour glucose and HbA1c for predicting the primary outcomes of all-cause mortality, cardiovascular mortality, cardiovascular events, heart disease events and stroke events. We also considered the secondary outcomes of heart failure, chronic kidney disease and retinopathy.

METHODS

Data sources and searches

We searched the electronic databases of Medline, PubMed, OVID and Cochrane for prospective cohort studies up to January 31, 2020. With the assistance of a certified librarian, we developed a search strategy (online supplemental table 1) using a combination of Medical Subject Headings and text search based on the following root terms: “prediabetes”, “intermediate hyperglycemia”, “impaired fasting glucose”, “IFG”, “impaired glucose tolerance”, “IGT”, “HbA1c”, “elevated HbA1c”, “raised HbA1c”, “glycosylated hemoglobin A1c”, “complication”, “mortality”, “cardiovascular disease or CVD”, “coronary heart disease or CHD”, “heart failure”, “heart attack”, “myocardial infarction”, “angina”, “ischemia”, “cardiac failure”, “cerebrovascular”, “revascularization”, “cerebral infarction”, “peripheral artery disease”, “retinopathy”, “neuropathy”, “polyneuropathy”, nephropathy“, “kidney or renal disease”, “CRD or CRF or CKF or CRF or CKD or ESKD or ESKF or ESRD or ESRF”, “microvascular”, “macrovascular”, “cancer”, “neoplasm”, “tumor” and “amputation”, “predict”, “association”, “prognosis”, “predictive model”, “prognostic model”, “predictive value”, “risk prediction”, “risk factor”, “risk score”.

Study selection

We identified 7153 studies for abstract screening. Studies were included for analysis if they met the following criteria: were prospective cohort studies of adult individuals aged 18 years and older, were from the general population or from patients with previous atherosclerotic CVD, had measures of impaired fasting glucose, impaired glucose tolerance or intermediate HbA1c as defined by the ADA, WHO or IEC criteria that was evaluated at baseline, included at least one outcome of interest, and

reported adjusted HRs, relative risks (RRs) or ORs for the risk of prediabetes and at at least one outcome of interest. Studies that did not have longitudinal measures of prediabetes as well as at least one relevant outcome, were not conducted in humans, and were not published in the English language were excluded from full-text review. A total of 280 studies were included in the full-text review. Of these, 174 studies were excluded for the following reasons; the study did not have a cut-point for intermediate hyperglycemia that was consistent with the WHO, ADA or IEC criteria: the study was an earlier version of a study included in the analysis; the study was a duplicate of another study included in the analysis; the study population had a pre-existing condition aside from atherosclerotic CVD; full-text of the study was not available; no relevant measures of association or CIs were reported; follow-up time was <2 years and no relevant outcome was reported. In total, 106 studies were included (online supplemental figure 1). Cohort studies were included multiple times if they assessed the associations between differing glycemic measures and outcomes. However, only the largest sample size of each cohort was counted towards the overall sample size of the analysis. Primary outcomes of interest were all-cause mortality, cardiovascular mortality, cardiovascular events, heart failure events and stroke events. Secondary outcomes of interest were heart failure, chronic kidney disease and retinopathy.

Our study protocol was developed in consensus with Emory investigators. This meta-analysis was not prospectively registered in the PROSPERO database.

Data extraction and quality assessment

Each title and abstract was screened independently by two reviewers (UPG, MH, SH, LRS, RJ, JW). Discrepancies were resolved by consensus or by a third reviewer. Full-text articles that met the inclusion criteria were obtained and study information such as sample size, mean age of participants, sex distribution, race/ethnicity, comorbidities, demographic characteristics and the relationship between non-diabetic glucose measures and outcomes were extracted independently by two reviewers on standard forms. The results were compared, and discrepancies were resolved by a third reviewer.

We used the Quality in Prognosis Studies Tool for study quality assessment. Validity and bias were judged on study participation, study attrition, prognostic factor measurement, confounding measurement and account, outcome measurement and analysis and reporting.[8] Two review authors independently rated the quality of evidence for each outcome (online supplemental table 2).

Data synthesis and analysis

We extracted the following information from each study: study characteristics (study name, author, publication year, pre-existing cardiovascular condition, location/region, follow-up time, sample size), participant's characteristics (mean age, gender distribution), primary and secondary outcomes (total mortality, CVD mortality, CVD events, heart disease events, stroke events, heart failure events, chronic kidney disease events and retinopathy). We also extracted point estimates (HRs, risk ratios or ORs) for the association between prediabetes and outcomes as well as all covariates included in the models. The data were entered into an excel spreadsheet specific for this study with an appropriate data validation feature to control the data type and value and to identify invalid entries. This study's primary purpose was to study the association between the differing definitions of intermediate hyperglycemia and all-cause and cardiovascular mortality, CVD, heart disease and stroke events compared with normoglycemia. CVD events were defined as the occurrence of more than one cardiovascular event. The secondary purpose was to compare the association between the differing definitions of intermediate hyperglycemia and heart failure, chronic kidney disease and retinopathy. The following definitions of intermediate hyperglycemia were used: IGT was defined as 140–199 mg/dL. IFG was defined according to the WHO criteria of 110–125 mg/dL (IFG WHO) or the ADA criteria of 100–125 mg/dL (IFG ADA).[1 2] Elevated HbA1c was defined by either the ADA definition of 5.7%–6.4% (HbA1c ADA) or the IEC definition of 6.0%–6.4% (HbA1c IEC).[4] Reference levels were normal glycemia as defined by each of the ADA, WHO or IEC criterion.

In this meta-analysis, the HRs and 95% CIs were appraised as the effect size for all the studies, and HRs were deemed equivalent to RRs. The formula RR=OR/([1−pRef]+[pRef×OR]), where pRef is the prevalence of the outcome in the reference group that was used to convert ORs to RRs for analysis.[9 10] Any results stratified by sex or race/ethnicity were handled as separate reports.

Summary HRs using both random-effects and fixed-effects models were obtained with the calculation of the logarithm of the HRs and corresponding 95% CIs of the individual studies. Forest plots were constructed to visually assess the pooled HRs and corresponding 95% CIs across studies. We explored the statistical heterogeneity across studies by I^2 statistic. Values of <25% were considered to represent a low likelihood of differences between studies, with values of 25%–75% representing a moderate likelihood, and those >75%–100% representing a high likelihood. A Cochran Q-test p<0.10 was considered indicative of statistically significant heterogeneity.[11] HRs were pooled using the fixed-effect model if no or low heterogeneity was observed. Otherwise, the DerSimonian and Laird random-effects model was used,[12] and the weights were equal to the inverse variance of each study's effect estimation. Publication bias was evaluated by inspecting funnel plots for each outcome in which the natural log RR was plotted against the SE and further tested with Egger's tests.

Sensitivity analysis was conducted after the removal of extreme effect sizes and by excluding each study sequentially by the leave-one-out diagnostics to evaluate whether a particular study may have strongly influenced the summary risk estimate.[13] In addition, a priori

Table 1 Associations between intermediate hyperglycemia and outcomes of interest

	IGT		IFG	HbA1c	
Comparison group	140 to 199 mg/dL	100 to 125 mg/dL	110 to 125 mg/dL	5.7% to 6.4%	6.0% to 6.4%
Referent group	<140 mg/dL	<100 mg/dL	<110 mg/dL	<5.7%	<6.0%
All-cause mortality	1.19 (1.15 to 1.24)	1.11 (1.04 to 1.19)	1.17 (1.13 to 1.22)	1.07 (0.97 to 1.18)	1.30 (1.03 to 1.66)
CVD mortality	1.21 (1.10 to 1.32)	1.14 (1.03 to 1.25)	1.20 (1.09 to 1.33)	1.20 (0.90 to 1.60)	1.07 (0.61 to 1.87)
CVD events	1.18 (1.11 to 1.26)	1.15 (1.05 to 1.25)	1.21 (1.09 to 1.33)	1.15 (1.02 to 1.30)	1.32 (1.00 to 1.73)
Stroke events	1.24 (1.06 to 1.45)	1.07 (0.95 to 1.07)	1.22 (1.07 to 1.40)	1.23 (1.04 to 1.46)	1.28 (0.72 to 2.27)
CHD events	1.13 (1.05 to 1.21)	1.10 (1.02 to 1.19)	1.14 (1.06 to 1.22)	1.28 (1.13 to 1.46)	1.33 (0.74 to 2.38)
Heart failure events	5.04 (1.00 to 25.4)	0.95 (0.84 to 1.07)	–	1.13 (0.87 to 1.45)	–
CKD	1.15 (0.95 to 1.39)	1.09 (1.01 to 1.18)	1.08 (0.91 to 1.28)	1.32 (1.16 to 1.50)	1.50 (1.32 to 1.70)
Retinopathy	–	1.11 (0.84 to 1.45)	–	0.84 (0.61 to 1.14)	–

CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; HbA1c, glycosylated hemoglobin A1c; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

subgroup analyses of primary and secondary outcomes were conducted according to region (North America vs others), and with pre-existing baseline conditions (yes/no).

All meta-analyses were conducted in R (V.3.5.1; R foundation of statistical computing, Vienna, Austria) statistical platform using the packages 'meta' (V.4.9–6)[14] and 'metafor' (V.2.1–0),[15] with a two-tailed α of 0.05 considered statistically significant.

RESULTS

Online supplemental table 3 details the key characteristics of all included studies. A majority of the cohorts came from Europe (n=39), Asia (n=28) and the USA (n=23). The duration of follow-up ranged from 2 to 33 years, with a mean duration of 9.57 years. According to quality assessment criteria (online supplemental table 2), the majority of studies were at low risk of bias.

The associations between intermediate hyperglycemia and the outcomes of interest are detailed in table 1.

Intermediate hyperglycemia and all-cause mortality

Of the 52 studies reporting the association between hyperglycemia and all-cause mortality, 25 examined the association of all-cause mortality with IGT, 25 examined the association with IFG ADA, 21 examined the association with IFG WHO, 14 examined the association with HbA1c 5.7%–6.4% and 3 examined the association with HbA1c 6.0%–6.4%. Compared with those with normal glucose tolerance, individuals with IGT; HR 1.19, 95% CI (1.15 to 1.24), IFG WHO; HR 1.17, 95% CI (1.13 to 1.22); IFG ADA; HR 1.11, 95% CI (1.04 to 1.19) and HbA1c 6.0%–6.4%; HR 1.30, 95% CI (1.03 to 1.66) had an increased risk for all-cause mortality (online supplemental figure 2). There was no evidence of an increased risk of all-cause mortality and HbA1c 5.7%–6.4%.

Online supplemental table 4 details the associations between all-cause mortality and intermediate hyperglycemia by presence of pre-existing CVD and region. There were significant differences in the association of IFG ADA and IFG WHO and all-cause mortality by presence of pre-existing condition. Those who had a pre-existing condition as well as prediabetes defined by the IFG ADA or the IFG WHO criteria had an increased risk of all-cause mortality compared with those in the general population. There were no significant differences in the association between prediabetes and all-cause mortality by pre-existing condition for IGT, HbA1c 6.0%–6.4% or HbA1c 5.7%–6.4%. There were no significant differences in the association of IFG ADA, IFG WHO or HbA1c 5.7%–6.4% and mortality by region. However, the association between IGT and mortality was increased among studies from Australia and Asia compared with the USA. HbA1c 6.0%–6.4% and mortality was increased among studies from the USA compared with Asia and Europe.

We found slight evidence of publication bias among studies assessing the association between all-cause mortality and intermediate hyperglycemia based on visual inspection of the funnel plot (online supplemental figure 9).

Intermediate hyperglycemia and cardiovascular mortality

Of the 41 studies reporting the association between intermediate hyperglycemia and cardiovascular mortality, 20 examined the association with IGT, 21 examined the association with IFG ADA, 17 examined the association with IFG WHO, 6 examined the association with HbA1c ADA and 1 examined the association with HbA1c IEC. Compared with those with normal glucose tolerance, individuals with IGT; HR 1.21, 95% CI (1.10 to 1.32), IFG WHO; HR 1.20, 95% CI (1.09 to 1.33) and IFG ADA; HR 1.14, 95% CI (1.03 to 1.25) had an increased risk for cardiovascular mortality (online supplemental figure 3). There was no evidence of an increased risk of cardiovascular mortality and HbA1c 5.7%–6.4% or HbA1c 6.0%–6.4%.

Those with IFG ADA and pre-existing CVD had an increased risk of cardiovascular mortality compared with those without pre-existing CVD. There were no significant differences in the association between prediabetes and

cardiovascular mortality by the presence of pre-existing CVD for those with IFG WHO, IGT, HbA1c 5.7%–6.4% or HbA1c 6.0%–6.4%. There were significant differences in the association between prediabetes and cardiovascular mortality by region. The association between IFG ADA and cardiovascular mortality was increased in cohorts from Europe and Asia compared with those from the USA. The association between HbA1c 5.7%–6.4% was increased in studies from the USA compared with Europe and Asia. There were no significant differences in the association between intermediate hyperglycemia and cardiovascular mortality by region using the IFG WHO, IGT or HbA1c 6.0%–6.4% cut-points (online supplemental table 4).

We found slight evidence of publication bias among studies assessing the association between cardiovascular mortality and intermediate hyperglycemia based on visual inspection of the funnel plot (online supplemental figure 10).

Intermediate hyperglycemia and incident cardiovascular disease

Of the 35 studies that reported the association between intermediate hyperglycemia and CVD, 17 examined the association with IGT, 24 examined the association with IFG ADA, 7 examined the association with IFG WHO, 13 examined the association with HbA1c 5.7%–6.4% and 4 examined the association with HbA1c 6.0%–6.4%. Compared with those with normal glucose tolerance, individuals with IGT; HR 1.18, 95% CI (1.11 to 1.26), IFG WHO; HR 1.21, 95% CI (1.09 to 1.33); IFG ADA; HR 1.15, 95% CI (1.05 to 1.25); HbA1c 5.7%–6.4%; HR 1.15, 95% CI (1.02 to 1.30) and HbA1c 6.0%–6.4%; HR 1.32, 95% CI (1.00 to 1.73) had an increased risk for cardiovascular events (online supplemental figure 4).

There were no significant differences in the association between prediabetes and cardiovascular events by presence of a pre-existing CVD. However, there were significant differences in the association between prediabetes and CVD by region among those with HbA1c 6.0%–6.4%. The association between CVD and HbA1c 6.0%–6.4% cut-points was increased in studies from the USA compared with those from Europe. There were no differnces in the association of IGT, IFG ADA, IFG WHO and HbA1c 5.7%–6.4% and CVD events by region.

We found no evidence of publication bias among studies assessing the association between CVD events and intermediate hyperglycemia based on visual inspection of the funnel plot (online supplemental figure 11).

Intermediate hyperglycemia and incident stroke

Of the 24 studies that reported the association between intermediate hyperglycemia and stroke, 10 examined the association with IGT, 15 examined the association with IFG ADA, 6 examined the association with IFG WHO, 5 examined the association with HbA1c 5.7%–6.4% and 1 examined the association with HbA1c 6.0%–6.4%. Compared with those with normal glucose tolerance, individuals with IGT; HR 1.24, 95% CI (1.06 to 1.45), IFG WHO; HR 1.22, 95% CI (1.07 to 1.40) and HbA1c 5.7%–6.4%; HR 1.23 95% CI (1.04 to 1.46) had an increased risk for stroke. There was no evidence of an increased risk of stroke and IFG ADA or HbA1c 6.0%–6.4% (online supplemental figure 5).

There were no significant differences in the association between prediabetes and incident stroke by presence of pre-existing CVD or geographic region.

We found moderate evidence of publication bias among studies assessing the association between incident stroke and intermediate hyperglycemia based on visual inspection of the funnel plot (online supplemental figure 12).

Intermediate hyperglycemia and incident heart disease

Of the 27 studies that reported the association between intermediate hyperglycemia and heart disease, 12 examined the association with IGT, 16 examined the association with IFG ADA, 9 examined the association with IFG WHO, 4 examined the association with HbA1c 5.7%–6.4% and 1 examined the association with HbA1c 6.0%–6.4%. Compared with those with normal glucose tolerance, individuals with IGT; HR 1.13, 95% CI (1.05 to 1.21), IFG WHO; HR 1.14, 95% CI (1.06 to 1.22); IFG ADA; HR 1.10, 95% CI (1.02 to 1.19) and HbA1c 5.7%–6.4%; HR 1.28, 95% CI (1.13 to 1.46) had an increased risk for heart disease. There was no evidence of an increased risk of heart disease and HbA1c 6.0%–6.4% (online supplemental figure 6).

There were no significant differences in the association between prediabetes and heart disease by presence of a pre-existing CVD. The association between heart disease and HbA1c 5.7%–6.4% was increased in studies from the USA compared with those from Europe or Asia. There were no differences in the association of IGT, IFG ADA, IFG WHO or HbA1c 6.0%–6.4% and heart disease events by region.

We found no evidence of publication bias among studies assessing the association between heart disease and intermediate hyperglycemia based on visual inspection of the funnel plot (online supplemental figure 13).

Intermediate hyperglycemia and incident heart failure, chronic kidney disease and retinopathy

The association between intermediate hyperglycemia and heart failure was examined in five studies. Of these, four examined the association with IFG ADA, one examined the association with IGT and two examined the association with HbA1c 5.7%–6.4%. Neither IFG ADA; HR 0.92, 95% CI (0.76 to 1.12) nor HbA1c 5.7%–6.4%; HR 1.13, 95% CI (0.87 to 1.18) were associated with an increased risk of heart failure. IGT was moderately significantly associated with increased risk of heart failure; HR 5.04, 95% CI (1.00 to 25.40) (online supplemental figure 7).

There were no significant differences in the association between prediabetes and incident heart failure by presence of pre-existing CVD or by region (online supplemental table 4).

We found evidence of possible publication bias in studies examining the association between intermediate hyperglycemia based on visual inspection of the funnel plot (online supplemental figure 14).

The association between incident chronic kidney disease and intermediate glycemia was examined in eight studies. Of those, five studies examined the association with IGT, four examined the association with IFG ADA, five examined the association with IFG WHO, three examined the association with HbA1c ADA and one assessed the association between HbA1c IEC and chronic kidney disease. IGT was associated with an increased risk of chronic kidney disease; HR 1.09, 95% CI (1.01 to 1.18). Both HbA1c 5.7%–6.4%; HR 1.32, 95% CI (1.16 to 1.50) and HbA1c 6.0%–6.4%; HR 1.50, 95% CI (1.32 to 1.70) were associated with an increased risk of chronic kidney disease. There were no significant associations with prediabetes as defined by the IFG ADA or IFG WHO criteria and chronic kidney disease (online supplemental figure 8).

All studies assessing the association between intermediate hyperglycemia and chronic kidney disease did so in participants with no history of baseline CVD. The association with IFG ADA and chronic kidney disease was increased in studies from the USA and the Middle East compared with those from Asia. The association between IFG WHO and chronic kidney disease was increased among studies from the USA compared with those from the Middle East or Asia. There were no significant differences in the association between intermediate hyperglycemia and chronic kidney disease by geographic region for either HbA1c criterion or IGT (online supplemental table 4).

There was some publication bias among studies assessing the association between chronic kidney disease and intermediate hyperglycemia based on visual inspection of the funnel plot (online supplemental figure 15).

Of the studies that met our inclusion criteria, one study examined the association between hyperglycemia and retinopathy for both IFG ADA and HbA1c ADA. Neither IFG ADA; HR 1.11, 95% CI (0.84 to 1.45) nor HbA1c ADA; HR 0.84, 95% CI (0.61 to 1.14) were associated with incident retinopathy.

DISCUSSION

The ADA and WHO currently differ in their definitions of intermediate hyperglycemia, and it is unclear how well various definitions of intermediate hyperglycemia predict risk for mortality and cardiovascular events. In this meta-analysis including 106 articles from inception to January 31, 2020, which comprised cohorts from 27 countries, and included 1 847 523 individuals, we found that the current definition of IGT was associated with a 19% increased risk of all-cause mortality, a 21% increased risk of cardiovascular mortality, a 18% increased risk of incident cardiovascular events, a 13% increased risk in incident heart disease and a 24% increased risk in incident stroke compared with normal glucose tolerance.

With regard to fasting glycemia, IFG as defined by the WHO criteria (110–125 mg/dL) was associated with an 17% increased risk of all-cause mortality, a 20% increased risk of CVD mortality, a 21% increased risk in incident cardiovascular events, a 14% increased risk in incident heart disease and a 22% increased risk in incident stroke. IFG as defined by the ADA criteria (100–125 mg/dL) was associated with an 11% increased risk of all-cause mortality, a 14% increased risk for cardiovascular mortality, a 15% increased risk for cardiovascular events, an 10% increased risk for heart disease, a 7% increased risk for stroke and a 9% increased risk for chronic kidney disease.

HbA1c 6.0%–6.4% was associated with a 30% increased risk of all-cause mortality, a 32% increased risk of CVD and a 50% increased risk of chronic kidney disease. HbA1c 5.7%–6.4% was associated with a 15% increased risk in CVD events, a 28% increased risk in heart disease, a 23% increased risk in stroke and a 32% increased risk in chronic kidney disease. There were not enough studies available to determine if prediabetes by any cut-point is significantly associated with increased risk of retinopathy

In recent years, a handful of meta-analyses have examined the associations between intermediate hyperglycemia and mortality or cardiovascular outcomes. A meta-analysis of 17 prospective cohort studies comprising 527 021 individuals found that the risk of incident coronary heart disease was increased in those with IFG as defined by both the ADA and WHO criteria.[16] Conversely, a meta-analysis of 15 studies including 760 925 individuals noted that IGT or a combination of IFG and IGT were associated with a moderately elevated risk of stroke incidence. However, IFG defined by the ADA criteria alone was not.[17] A previous meta-analysis conducted by Huang *et al* similarly examined the association between intermediate hyperglycemia[18] and composite cardiovascular events and all-cause mortality, and noted that both IGT and IFG were associated with an increased risk of the outcomes of interest. A recently updated analysis of the Huang study by Cai *et al* examined the association between prediabetes and the risk of all-cause mortality and incident CVD in the general population and in patients with a history of atherosclerotic CVD in 10 069 955 individuals from 129 studies.[19] Results of this study found that prediabetes was associated with an increased risk of all-cause mortality and CVD in both the general population and in patients with atherosclerotic CVD.[19] Our study adds further evidence to support the notion that prediabetes is an increased risk state for mortality and cardiovascular events. We also found that prediabetes may be an increased risk for chronic kidney disease, particularly by the HbA1c ADA or HbA1d IEC criteria.

Current recommendations to identify intermediate hyperglycemia are inconsistent and controversial. Both the WHO and ADA criteria for IFG are based on studies assessing the lower limits of fasting glucose above which

the risk for developing diabetes increases considerably.[20] The lower limit of IFG was originally set at 110 mg/dL, which is still the cut-point accepted by WHO,[2] and was based on an analysis of the Paris Prospective Study which reported that a fasting plasma glucose range between 110 and 126 mg/dL was similar to IGT in terms of predicting future diabetes prevalence.[20] In 2003, the ADA lowered the cut-point for IFG to 100 mg/dL based on analyses of data from four populations: Pima Indian, Mauritius, San Antonio and Dutch.[21] Results of these analyses indicated that 110 mg/dL was inappropriately high as the lower limit for IFG and suggested that a cut-point of 100 mg/dL would optimise the sensitivity and specificity for diabetes prediction.[21] The results of our study found evidence of increased risk of all-cause mortality, CVD mortality, CVD, heart disease and stroke at both the IFG ADA and the IFG WHO cut-points.

In addition, the use of HbA1c to identify intermediate hyperglycemia is also controversial given that the ADA suggests a cut-point of HbA1c 5.7%–6.4% for intermediate hyperglycemia, while an IEC[4] as well as the UK-based National Institute for Health and Clinical Excellence[5] both recommend using HbA1c 6.0%–6.4%, and WHO currently does not offer any interpretation of HbA1c levels below 6.5%.[22] In our study, we found that the higher cut-point of 6.0%–6.4% was associated with an increased risk of all-cause mortality, and chronic kidney disease, while the lower cut-point of 5.7%–6.4% was associated with an increased rsk of cardiovascular events, heart disease, stroke and chronic kidney disease. These results provide evidence to support the inclusion of HbA1c as a definition for prediabetes. However, few studies examined the relationship between HbA1c 6.0%–6.4% and mortality, cardiovascular outcomes, chronic kidney disease or retinopathy, and additional studies are needed to determine the association between HbA1c 6.0%–6.4% and adverse outcomes.

The results of our study should be interpreted in the context of limitations. All studies included were observational studies. Therefore, we cannot draw definitive causal associations, given that some studies may be subject to bias unaccounted for in the adjustment for confounding. There is also heterogeneity in the included study populations, follow-up times, outcome definitions and model specifications. In addition, many studies did not assess the isolated forms of IFG glucose, IGT or elevated HbA1c. Therefore, it is possible that studies assessing the risk of outcomes in individuals with IFG could also be including individuals with IGT or elevated HbA1c. Additionally, while we had data from 27 individual countries, the majority of studies came from Asia, Europe and the USA. Many regions, including the majority of South Asia, Africa and South and Central America were not represented. It is possible that the results would differ had there been more data from those regions. Lastly, the majority of the studies assessed the relationship between intermediate hyperglycemia and all-cause mortality, cardiovascular mortality, cardiovascular events or heart disease. Additional research is needed to assess the strength of the association between intermediate hyperglycemia and heart failure, chronic kidney disease and retinopathy. However, our study also has several strengths. We included data from nearly 1.85 million individuals from 27 different countries, and were therefore able to assess the associations with varying types of prediabetes and the risk of mortality, CVD as well as microvascular outcomes such as chronic kidney disease. Lastly, the majority of the studies included in our analysis were of high quality and adequately adjusted for confounders.

In summary, the findings of our study note that IGT, as currently defined, adequately indicates increased risk for all-cause mortality, CVD mortality, incident cardiovascular events, incident heart disease and incident stroke. Furthermore, fasting glucose levels between 110 and 125 mg/dL as well as those between 100 and 125 mg/dL were associated with an increased risk of mortality and cardiovascular events. However, compared with IFG ADA, IFG WHO was associated with an increased risk of all-cause mortality, CVD mortality, cardiovascular events, heart disease and stroke. Lastly, HbA1c levels 6.0%–6.4% were associated with an increased risk of mortality and chronic kidney disease while HbA1c 5.7%–6.4% was associated with an increased risk of cardiovascular events, heart disease, stroke and chronic kidney disease. Our results indicate that prediabetes by IGT, IFG and HbA1c criteria is an increased risk state for mortality, cardiovascular and microvascular outcomes.

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Contributors UPG contributed to the study inception and design, screening and extracting data, data interpretation and manuscript writing and editing. RJ was responsible for data screening and extraction, data analysis, data interpretation and manuscript editing. SH was responsible for data screening and extraction, the preparation and design of tables and figures and manuscript editing. MH was responsible for data screening and extraction, data analysis and manuscript editing. LRS and JW were responsible for data screening and extraction and manuscript editing. NS was responsible for data cleaning and organization. KMVN was responsible for study inception and design, data interpretation and manuscript editing. UPG had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethics approval was not required for this analysis.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as supplemental information.

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Supplemental Table 1. Search Strategy

PubMed = 506 (? minus duplicates) 1/31/2020

(prediabet*[tw] OR pre-diabet*[tw] OR elevated hba1c[tw] OR raised hba1c[tw] OR impaired fasting glucose[tw] OR intermediate hyperglycemia[tw] OR impaired glucose tolerance[tw] OR impaired fasting plasma glucose[tw] OR elevated glycosylated hemoglobin a1c[tw] OR raised glycosylated hemoglobin a1c[tw])

AND

(complication[tw] OR mortality[tw] OR chd[tw] OR cvd[tw] OR coronary artery disease[tw] OR Coronary event[tw] OR coronary syndrome [tw] or heart muscle ischemia[tw] OR heart failure[tw] OR heart attack[tw] OR heart infarction[tw] OR myocardial infarct*[tw] OR cardiac failure[tw] OR angina pectoris[tw] OR angina[tw] OR revasculari*[tw] OR cerebrovascular accident[tw] OR cerebrovascular stroke[tw] or strokes[tw] OR cerebrovascular[tw] OR brain infarction[tw] OR brain ischemia[tw] OR apoplexy[tw] OR peripheral vascular disease[tw] OR cardiovascular disease[tw] OR neuropathy[tw] OR polyneuropathy[tw] OR retinopathy[tw] OR retina maculopathy[tw] OR kidney disease[tw] OR kidney failure[tw] OR nephropathy[tw] OR nephrotic[tw] OR proteinuria[tw] OR albuminuria[tw] OR renal disease[tw] OR renal failure[tw] OR kidney graft[tw] OR kidney transplantation[tw] OR renal transplantation[tw] OR crk[tw] OR ckf[tw] OR crf[tw] OR ckd[tw] OR eskd[tw] OR eskf[tw] OR esrd[tw] OR esrf[tw] OR microvascular[tw] OR macrovascular[tw] OR cancer[tw] OR carcino*[tw] OR neoplas*[tw] OR tum*r* [tw] OR amputation[tw] OR ulcer[tw] OR foot[tw] or feet[tw] OR wound[tw])

AND

(predict*[tw] OR associa*[tw] OR prognos*[tw] OR predictive model[tw] OR prognostic model[tw] OR predictive value[tw] OR risk prediction[tw] OR risk factor[tw] OR risk factor[tw] OR risk score[tw])

NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))

NOT Medline[sb]

Embase = 3272 (¿ minus duplicates) 1/31/20

prediabet* OR 'pre diabet*' OR 'elevated hba1c' OR 'raised hba1c' OR 'impaired fasting glucose'/de OR 'impaired fasting glucose' OR 'intermediate hyperglycemia' OR 'impaired glucose tolerance'/de OR 'impaired glucose tolerance' OR 'impaired fasting plasma glucose' OR 'elevated glycosylated hemoglobin a1c' OR 'raised glycosylated hemoglobin a1c'

((((((((((('complication'/de OR 'complication' OR 'mortality'/de OR 'mortality' OR chd OR cvd OR 'coronary artery disease'/de OR 'coronary artery disease' OR coronary) AND event OR coronary) AND ('syndrome' OR 'syndrome'/de OR syndrome) OR 'heart muscle ischemia'/de OR 'heart muscle ischemia' OR 'heart failure'/de OR 'heart failure' OR 'heart' OR 'heart'/de OR heart) AND attack OR 'heart' OR 'heart'/de OR heart) AND ('infarction' OR 'infarction'/de OR infarction) OR myocardial) AND infarct* OR cardiac) AND ('failure' OR 'failure'/de OR failure) OR 'angina pectoris'/de OR 'angina pectoris' OR 'angina' OR 'angina'/de OR angina OR revasculari* OR 'cerebrovascular accident'/de OR 'cerebrovascular accident' OR 'stroke' OR 'stroke'/de OR stroke OR strokes OR cerebrovascular OR 'brain infarction'/de OR 'brain infarction' OR 'brain ischemia'/de OR 'brain ischemia' OR 'apoplexy' OR 'apoplexy'/de OR apoplexy OR vascular) AND ('artery' OR 'artery'/de OR artery) AND ('disease' OR 'disease'/de OR disease) OR 'peripheral vascular disease'/de OR 'peripheral vascular

disease') AND ('cardiovascular disease'/de OR 'cardiovascular disease') OR 'neuropathy'/de OR 'neuropathy' OR 'polyneuropathy'/de OR 'polyneuropathy' OR 'retinopathy'/de OR 'retinopathy' OR 'retina maculopathy'/de OR 'retina maculopathy' OR 'kidney disease'/de OR 'kidney disease' OR 'kidney failure'/de OR 'kidney failure' OR 'nephropathy' OR 'nephropathy'/de OR nephropathy OR nephrotic OR 'proteinuria'/de OR 'proteinuria' OR 'albuminuria'/de OR 'albuminuria' OR renal) AND ('disease' OR 'disease'/de OR disease) OR renal) AND ('failure' OR 'failure'/de OR failure) OR 'kidney graft'/de OR 'kidney graft' OR 'kidney transplantation'/de OR 'kidney transplantation' OR renal) AND ('transplantation' OR 'transplantation'/de OR transplantation) OR renal) AND ('transplant' OR 'transplant'/de OR transplant) OR crk OR ckf OR 'crf' OR 'crf'/de OR crf OR ckd OR eskd OR eskf OR 'esrd' OR 'esrd'/de OR esrd OR esrf OR mcrivascular OR macrovascular OR 'malignant neoplasm'/de OR 'malignant neoplasm' OR 'cancer' OR 'cancer'/de OR cancer OR carcino* OR neoplas* OR tum*r* OR 'amputation'/de OR 'amputation' OR 'ulcer'/de OR 'ulcer' OR 'foot'/de OR 'foot' OR feet OR 'wound' OR 'wound'/de OR wound

predict* OR associa* OR prognos* OR 'predictive model'/de OR 'predictive model' OR 'prognostic model'/de OR 'prognostic model' OR 'predictive value'/de OR 'predictive value' OR 'risk prediction'/de OR 'risk prediction' OR 'risk factor'/de OR 'risk factor' OR 'risk score'/de OR 'risk score'

#1 AND #2 AND #3

#4 NOT ([animals]/lim NOT [humans]/lim)

Cochrane = 11 (¿ minus duplicates) 1/31/2020

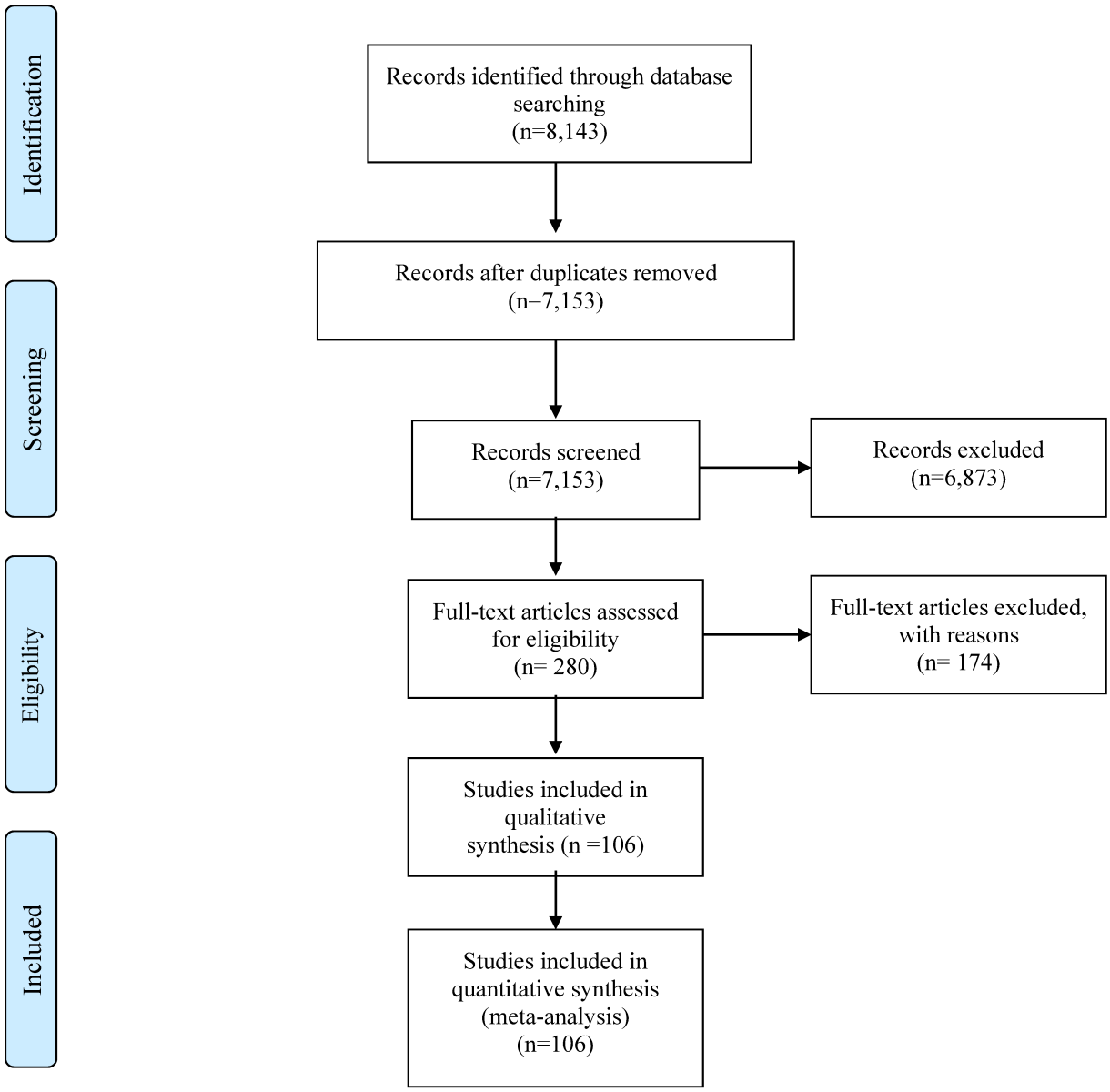
(prediabetes OR prediabetic OR "pre diabetes" OR "pre diabetic" OR "intermediate hyperglycemia" OR "intermediate hyperglycaemia" OR "intermediate hyperglycemic" OR "intermediate hyperglycaemic" OR "impaired glucose tolerance" OR "impaired fasting glucose") AND (complication OR complications OR mortality OR CHD OR CVD OR coronary OR heart OR myocardial OR infarct OR infarction OR infarcts OR infarctions OR ischemia OR ischemic OR ischaemia OR ischaemic OR failure OR angina OR revascularization OR revascularisation OR revascularizations OR revascularisations OR stroke OR strokes OR cerebrovascular OR apoplexy OR vascular or peripheral OR cardiovascular OR neuropathy OR neuropathies OR polyneuropathy OR polyneuropathies OR retinopathy OR retinopathies OR maculopathy OR maculopathies OR nephropathy OR nephropathies OR nephrotic OR proteinuria OR proteinuric OR albuminuria OR kidney OR renal OR CRD OR CRF OR CKF OR CRF OR CKD OR ESKD OR ESKF OR ESRD OR ESRF OR microvascular OR macrovascular OR "micro vascular" OR "macro vascular" OR cancer OR carcinoma OR neoplasm OR neoplasms OR tumor OR tumors OR tumour OR tumours OR amputation OR amputations OR ulcer OR foot OR feet OR wounds)

OVID Medline = 4299 (¿ minus duplicates) 1/31/2020

Prediabetic state/
(prediabet* or pre diabet*).tw.
intermediate hyperglyc?emi*.tw.
(elevated hba1c or raised hba1c or impaired fasting glucose or intermediate hyperglycemia or impaired glucose tolerance or impaired fasting plasma glucose or elevated glycosylated hemoglobin a1c or raised glycosylated hemoglobin a1c).tw.
1 or 2 or 3 or 4

(predict* or associa* or prognos* or predictive model or prognostic model or predictive value or risk prediction or risk factor or risk factor or risk score).tw.
exp Mortality/
complication?.tw.
mortality.tw.
(CHD or CVD).tw.
(coronary adj2 disease).tw.
(coronar* adj (event? or syndrome?)).tw.
(heart adj (failure or disease? or attack? or infarct*)).tw.
(myocardial adj (infarct* or isch?emi*)).tw
cardiac failure.tw.
angina.tw.
revasculari*.tw.
(stroke or strokes).tw.
cerebrovascular.tw.
((brain* or cerebr*) adj (infarct* or isch?emi*)).tw.
apoplexy.tw.
((vascular or peripheral arter*) adj disease?).tw.
cardiovascular.tw.
(neuropath* or polyneuropath*).tw.
(retinopath* or maculopath*).tw.
(nephropath* or nephrotic or proteinuri* or albuminuri*).tw.
((kidney or renal) adj (disease? or failure or transplant*)).tw.
((chronic or endstage or end stage) adj (renal or kidney)).tw.
(CRD or CRF or CKF or CRF or CKD or ESKD or ESKF or ESRD or ESRF).tw.
(microvascular or macrovascular or ((micro or macro) adj vascular)).tw.
(cancer or carcino* or neoplas* or tumo?r?).tw.
(amputation? or ulcer* or foot or feet or wound*).tw.
or/7-32
5 and 6 and 33
exp animals/ not humans/
34 not 35
(comment or letter or editorial).pt.
36 not 37

Supplemental Figure 1. Flow Diagram of Included Studies



Supplemental Table 3. Bias Assessment of Included Studies

	Domains of bias evaluation (low, moderate, or high risk of bias [1-6])					
Author, Year	**Study participants**	**Study attrition**	**Prognostic factor measurement**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
Stengard, 1993	Low	Low	Low	Low	Low	Low
Barzilay, 1999	Low	Low	Low	Low	Low	Low
Saydah, 2001	Low	Low	Low	Low	Low	Low
Mazza, 2001	Low	Low	High	Low	Moderate	Moderate
Rodriguez, 2002	Low	Low	Low	Low	Low	Moderate
Henry, 2002	Low	Low	Low	Low	Low	Low
Hu / DECODE group, 2003	Low	Low	Low	Low	Low	Low
Lu, 2003	Low	Low	Low	Low	Low	Low
Ma, 2003	Low	Low	Low	Low	Low	Low
Nakanishi, 2004	High	Low	Low	Low	Low	Low
Wild, 2005	Low	Low	Low	Low	Low	Low
Hiltunen, 2005	Low	Low	Low	Low	Low	Low
Kanaya, 2005	Low	Low	Low	Low	Low	Low
Fox, 2005	Low	Low	Low	Low	Low	Low
Wang, 2006	Low	Moderate	Low	Low	Low	Low
Kaarisalo, 2006	Low	Low	Low	Low	Low	Low
Tozawa, 2007	Low	Low	Low	Low	Low	Low
Barr, 2007	Low	Low	Low	Low	Low	Low
Rijkelijkhuizen, 2007	Low	Low	Low	Low	Low	Low
Pankow, 2007	Low	Low	Low	Low	Low	Low
Nielson, 2007	Low	Low	Low	Low	Low	Low
Nigam, 2007	Low	Low	Low	Low	Low	Low
Tsai, 2008	Low	Low	Low	Low	Low	Low
Chien, 2008	Low	Low	Low	Low	Low	Low

Supplemental Table 3. Bias Assessment of Included Studies

	Domains of bias evaluation (low, moderate, or high risk of bias [1-6])					
Author, Year	**Study participants**	**Study attrition**	**Prognostic factor measurement**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
Oizumi, 2008	Low	Low	Low	Moderate	Moderate	Moderate
Zhang, 2009	Low	Low	Low	Low	Low	Moderate
Hyvärinen, 2009	Low	Moderate	Low	Low	Low	Low
Kokubo, 2010	Low	Low	Low	Low	Low	Low
Skriver, 2010	Moderate	Low	Low	Moderate	Low	Low
Watanabe, 2010	Low	Low	Low	Moderate	Low	Low
Cederberg, 2010	Low	Low	Low	Low	Low	Moderate
Magliano, 2010	Low	Low	Moderate	Low	Low	Low
Sui, 2011	Low	Low	Low	Low	Low	Low
Donahue, 2011	Moderate	Low	Low	Low	Moderate	Low
Saito, 2011	Low	Low	Low	Moderate	Moderate	Low
Tamita, 2012	Moderate	Low	Low	Low	Low	High
Yeboah, 2012	Low	Low	Low	Low	Low	Low
Intzilakis, 2012	Low	Low	Low	Low	Low	Low
Madssen, 2012	Low	Low	High	Low	Low	Low
Laukkanen, 2013	Moderate	Low	Low	Low	Low	Low
Schöttker, B 2013	Low	Low	Low	Low	Low	Low
Selvin, 2013	Low	Low	Low	Low	Low	Low
Deedwania, 2013	Low	Low	Low	Moderate	Low	Low
Selvin, 2011	Low	Low	Low	Low	Low	Low
Onat, 2013	Low	Low	High	Low	Low	High
Kim, 2014	Low	Low	Low	Moderate	Moderate	Moderate
Mainous, 2014	Low	Low	Low	Low	Low	Low
Shi, 2015	Low	Low	Low	Low	Low	Low
Bergman, 2015	Low	Moderate	Low	Low	Low	Low

Supplemental Table 3. Bias Assessment of Included Studies

	Domains of bias evaluation (low, moderate, or high risk of bias [1-6])					
Author, Year	**Study participants**	**Study attrition**	**Prognostic factor measurement**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
Qiu, 2015	Low	Low	Low	Low	Low	Low
Rebnord, 2015	Moderate	Low	Low	Low	Low	Low
Eastwood, 2015	Low	Low	Low	Low	Low	Low
Paprott, 2015	Low	Low	Low	Low	Low	Low
Gordon-Dseagu, 2015	Low	Moderate	Low	Low	Low	Low
Kim, 2016	Low	Low	Low	Moderate	Low	Low
Rhee, 2016	Low	Low	Low	Low	Low	Low
Parrinello, 2016	Low	Low	Low	Low	Low	Low
Khosravi, 2016	Low	Low	Low	Moderate	Moderate	Moderate
Salazar, 2016	Low	Low	Low	Moderate	Moderate	Moderate
Mirbolouk, 2016	Low	Low	Low	Low	Low	Low
Warren, 2017	Low	Low	Low	Low	Low	Low
Silbernagel, 2011	Low	Low	Low	Low	Low	Low
Ares, 2019	Low	Low	Low	Low	Low	Low
Chattopadhyay, 2019	Moderate	Moderate	Low	Low	Low	Low
Chen, 2018	Moderate	Low	Low	Low	Low	Low
de Abreu, 2017	Low	Low	Low	Low	Low	Low
Fang, 2019	Low	Low	Low	Low	Low	Low
Doi, 2010	Low	Low	Low	Low	Low	Low
Fisman, 2001	Moderate	Low	Low	Low	Low	Low
George, 2015	Moderate	Low	Low	Low	Low	Low
Hajebrahimi, 2017	Moderate	Low	Low	Low	Low	Low
Hermanides, 2019	Low	Low	Low	Low	Low	Low
Hubbard, 2019	Low	Low	Low	Low	Low	Low
Janszky, 2008	Low	Low	Low	Low	Low	Low

Supplemental Table 3. Bias Assessment of Included Studies

	Domains of bias evaluation (low, moderate, or high risk of bias [1-6])					
Author, Year	**Study participants**	**Study attrition**	**Prognostic factor measurement**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
Jiang, 2019	Low	Low	Low	Low	Low	Low
Khang, 2010	Low	Low	Low	Low	Low	Low
Kim, 2019	Low	Low	Low	Low	Low	Low
Kowall, 2011	Low	Low	Low	Low	Low	Low
Liu, 2018	Moderate	Low	Low	Low	Low	Low
Liu, 2007	Low	Low	Low	Low	Low	Low
Lu, 2019	Low	Low	Low	Low	Low	Low
Ma, 2012	Low	Low	Low	Low	Low	Low
Michishita, 2017	Low	Low	Low	Low	Low	Low
Palmieri, 2006	Low	Low	Low	Low	Low	Low
Parizadeh, 2019	Low	Low	Low	Low	Low	Low
Pavlovic, 2019	Moderate	Low	Low	Low	Low	Low
Robich, 2019	Moderate	Low	Low	Low	Low	Low
Rutten-Jacobs, 2014	Moderate	Low	Low	Low	Low	Low
Samaras, 2015	Low	Low	Low	Low	Low	Low
Stacey, 2019	Low	Low	Low	Low	Low	Low
Tai, 2004	Low	Low	Low	Low	Low	Low
Thrainsdottir, 2005	Low	Low	Low	Low	Low	Low
Nakagami, 2004	Low	Low	Low	Low	Low	Low
Vistisen, 2018	Low	Low	Low	Low	Low	Low
Wang, 2008	Low	Low	Low	Low	Low	Low
Welsh, 2020	Low	Low	Low	Low	Low	Low
Neves, 2020	Low	Low	Low	Low	Low	Low
Kim, 2008	Low	Low	Low	Low	Moderate	Low
Brunner, 2010	Low	Low	Low	Low	Low	Low

Supplemental Table 3. Bias Assessment of Included Studies

	Domains of bias evaluation (low, moderate, or high risk of bias [1-6])					
Author, Year	**Study participants**	**Study attrition**	**Prognostic factor measurement**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**
Hunt, 2010	Low	Low	Low	Low	Low	Low
Farhan, 2019	Moderate	Low	Low	Low	Low	Low
Evans, 2015	Low	Low	Low	Low	Low	Low
Bjarnason, 2019	Moderate	Low	Low	Low	Low	Low
Wang, 2008	Low	Low	Low	Low	Low	Low
Ding, 2014	Moderate	Low	Low	Low	Low	Low
McNeill, 2006	Low	Low	Low	Low	Low	Low

1. Study participants: high bias – the relationship between predictor and outcome is very likely to be different for participants and eligible nonparticipants. Moderate bias – the relationship may be different. Low bias – the relationship is unlikely to be different.
2. Study attrition: high bias – the relationship between predictor and outcome is very likely to be different for completing and non-completing participants. Moderate bias – the relationship may be different. Low bias – the relationship is unlikely to be different.
3. Prognostic factor measurement: high bias – the measurement of the predictor is very likely to be different related to the baseline level of the predictor. Moderate bias – the measurement may be different. Low bias – the measurement is unlikely to be different.
4. Outcome measurement: high bias – the measurement of the outcome is very likely to be different for different levels of the outcome of interest. Moderate bias – the measurement may be different. Low bias – the measurement is unlikely to be different.
5. Study confounding: high bias – the observed effect of the predictor on the outcome is very likely to be distorted by another factor related to the predictor and outcome. Moderate bias – the effect may be distorted. Low bias – the effect is unlikely to be distorted.
6. Statistical analysis and reporting: high bias – the reported results are very likely to be spurious or biased related to analysis or reporting. Moderate bias may be spurious or biased. Low bias – unlikely to be spurious or biased.

Supplemental Table 2. Study characteristics of all included studies

Author, Year	Country	Prediabetes Definition	Sample Size	% Female	Mean Age or Age Range (y)	Follow Up (y)	Outcome(s) of interest
Stengard, 1992 [23]	Finland	IGT	716	0.00%	72.4	5	All-cause mortality, CVD mortality
Barzilay, 1999 [24]	USA	IFG (ADA), IGT	4515	58.00%	73	8	CVD events
Saydah, 2001 [25]	USA	IFG (ADA, WHO), IGT	3092	53.90%	48.8	16	All-cause mortality, CVD mortality
Mazza, 2001 [26]	Italy	IGT	3382	61.00%	73.8	14	CVD mortality
Rodriguez, 2002 [27]	USA	IFG (ADA and WHO), IGT	2034	0.00%	71-93 (range)	7	All-cause mortality, CVD mortality
Henry, 2002 [28]	France	IFG (WHO)	63443	0.00%	21-60 (range)	8	All-cause mortality, CVD mortality
Hu, 2003 [29]	Europe (Finland, Sweden, Poland, United Kingdom, Denmark, Netherlands, and Italy)	IFG (WHO), IGT	17579	53.50%	30-89 (range)	8.3	All-cause mortality, CVD mortality
Lu, 2003 [30]	USA	IFG (WHO)	4303	56.10%	56	9	All-cause mortality, CVD mortality
Ma, 2003 [31]	Singapore	IGT, IFG (WHO)	3492	56.90%	18-69 (range)	9	All-cause mortality
Nakanishi, 2004 [32]	Japan	IFG (WHO)	5588	0.00%	47.2	7	CVD events
Wild, 2005 [33]	United Kingdom	IFG (WHO), IGT	1592	49.20%	64.8	12.6	All-cause mortality, CVD mortality
Hiltunen, 2005 [34]	Finland	IGT	379	63.00%	76.3	9.8	All-cause mortality
Kanaya, 2005 [35]	USA	IFG (ADA)	2321	100.00%	65	6.8	CVD mortality, CVD events, Stroke, CHD
Fox, 2005 [36]	USA	IFG (ADA), IGT	2398	53.00%	54	7	CKD
Wang, 2006 [37]	China	IFG (ADA and WHO), IGT	541	49.90%	47.8	5	CHD
Kaarisalo, 2006 [38]	Finland	IGT	1032	51.80%	70	12	Stroke
Tozawa, 2007 [39]	Japan	IFG (WHO)	8151	36.00%	49	5	CKD
Barr, 2007 [40]	Australia	IFG (WHO), IGT	10428	54.80%	51.4	5.2	All-cause mortality, CVD mortality
Rijkelijkhuizen, 2007 [41]	The Netherlands	IFG (ADA and WHO)	1428	54.00%	60.5	6.4	All-cause mortality, CVD mortality
Pankow, 2007 [42]	USA	IGT	6888	41.40%	62.3	6.3	CHD
Nielson, 2007 [43]	USA	IFG (ADA)	28477	6.10%	57.1	8	Stroke
Nigam, 2007 [44]	USA and Canada	IFG (WHO), IGT	13176	23.70%	52.5	14.7	All-cause mortality, CVD mortality, CVD events
Tsai, 2008 [45]	Taiwan	IFG (WHO)	35259	34.20%	52.4	15	All-cause mortality, CVD mortality

Chien, 2008 [46]	Taiwan	IFG (WHO), IGT	2165	56.00%	54.2	10.5	CVD events
Oizumi, 2008 [47]	Japan	IGT	3482	56.00%	57.2	9.7	CVD events, Stroke, CHD
Zhang, 2009 [48]	USA	IGT	4549	59.40%	45-74 (range)	13.4	Stroke
Hyvärinen, 2009 [49]	Finland, Sweden	IFG (WHO), IGT	18360	45.60%	25-90 (range)	12.9	Stroke
Kokubo, 2010 [50]	Japan	IFG (ADA)	5069	54.00%	54.3	11.7	CVD events, Stroke
Skriver, 2010 [51]	Denmark	HbA1c (IEC)	23783	53.60%	54.9	8	All-cause mortality
Watanabe, 2010 [52]	Japan	IGT	34986	66.00%	59	5.8	CKD
Cederberg, 2010 [53]	Finland	IGT, HbA1c (ADA)	553	59.70%	61	10	CVD events
Magliano, 2010 [54]	Mauritius	IFG (WHO), IGT	9091	54.10%	41	15.1	All-cause mortality, CVD mortality
Selvin, 2011 [55]	USA	IFG (ADA), HbA1c (ADA)	9170	57.30%	56.7	14	CKD, Retinopathy
Sui, 2011 [56]	USA	IFG (WHO)	43933	0.00%	44.3	31	CVD mortality, Stroke
Donahue, 2011 [57]	USA	IFG (ADA)	1256	27.70%	55.1	3.5	CVD events
Saito, 2011 [58]	Japan	IFG (ADA), IGT	31192	63.70%	53.3	12.9	CVD mortality, CHD
Tamita, 2012 [59]	Japan	IFG (WHO)	275	22.00%	61.9	5	CVD events
Yeboah, 2012 [60]	USA	IFG (ADA)	7932	51.00%	62	7.5	All-cause mortality, CVD events, CHD, Stroke
Intzilakis, 2012 [61]	Denmark	IFG (ADA)	2373	42.80%	64.4	6.3	CVD events
Madssen, 2012 [62]	Norway	IFG (WHO), IGT	47951	51.60%	60	12	CVD mortality
Laukkanen, 2013 [63]	Finland	IFG (ADA)	2486	0.00%	52.9	20.7	All-cause mortality, CVD mortality
Schöttker, 2013 [64]	Germany	IFG (ADA), HbA1c (ADA)	9451	55.10%	62	7.9	CVD events
Selvin, 2013 [65]	USA	IFG (ADA), HbA1c (ADA)	11077	57.70%	56.7	18	CVD mortality
Deedwania, 2013 [66]	USA	IFG (ADA)	2842	57.00%	73	13	All-cause mortality, CVD mortality, Stroke, Heart Failure
Onat, 2013 [67]	Turkey	IFG (WHO)	2619	51.30%	47.8	7.5	CHD
Kim, 2014 [68]	South Korea	IGT	3376	59.70%	50.3	11	All-cause mortality, CVD mortality
Mainous, 2014 [69]	USA	HbA1c (ADA)	8003	53.10%	≥ 40	12.5	All-cause mortality
Shi, 2015 [70]	China	IFG (ADA)	2849	45.90%	47	10	All-cause mortality, CVD mortality
Bergman, 2015 [71]	Israel	IFG (ADA), IGT	1410	47.80%	53.1	33	All-cause mortality
Qiu, 2015 [72]	China	IFG (ADA), IGT	1419	58.80%	54.2	10.9	CVD events
Rebnord, 2015 [73]	Norway	HbA1c (ADA)	2519	27.00%	62	4.8	All-cause mortality, CVD mortality, CVD events
Eastwood, 2015 [74]	United Kingdom	IFG (WHO), IGT, HbA1c (IEC, ADA)	2477	16.30%	51.6	20	CVD events, CHD, Stroke

Paprott, 2015 [75]	Germany	HbA1c (ADA)	6299	50.80%	45.8	11.6	All-cause mortality
Gordon-Dseagu, 2015 [76]	United Kingdom	HbA1c (ADA)	22106	54.00%	52	7	All-cause mortality, CVD mortality
Kim, 2016 [77]	South Korea	IFG (ADA), HbA1c (ADA)	76434	42.80%	47.5	3.1	All-cause mortality CVD events, Stroke, Heart Disease
Rhee, 2016 [78]	South Korea	IFG (ADA), HbA1c (ADA)	241499	45.40%	39.7	3.8	All-cause mortality, CVD mortality
Parrinello, 2016 [79]	USA	IFG (ADA), HbA1c (ADA)	10373	57.90%	57.1	20	CHD, Stroke, Heart Failure
Khosravi, 2016 [80]	Iran	IFG (ADA), IGT	5398	51.50%	50.8	10	CVD events, Stroke, Heart Disease
Salazar, 2016 [81]	Argentina	IFG (ADA)	664	69.20%	52.5	8	CVD events
Mirbolouk, 2016 [82]	Iran	IFG (ADA), IGT	922	42.30%	69.8	9	CVD mortality
Warren, 2017 [83]	USA	IFG (ADA, WHO), IGT, HbA1c (ADA, IEC)	10844	56.90%	57.2	24	All-cause mortality, CVD events, CKD
Silbernagel, 2011 [84]	Germany	IFG (ADA)	3316	29.40%	61.8	7.5	All-cause mortality, CVD mortality
Ares, 2019 [85]	Spain	IGT, IFG (ADA), HbA1c (ADA)	1,034	54.3	52.1	18	All-cause mortality, CVD mortality
Chattopadhyay, 2019 [86]	United Kingdom	IFG (ADA), IGT	850	29%	63.6	2.8	CVD event
Chen, 2018 [87]	China	IFG (ADA)	587	34%	64.9	7	All-cause mortality, CVD mortality
de Abreu, 2017 [88]	Australia	IFG (ADA)	1167	100%	48.6	10	All-cause mortality
Fang, 2019 [89]	China	IGT	460	0%	72.1	11.2	All-cause mortality, CVD events, CHD, Stroke, Heart Failure
Doi, 2010 [90]	Japan	IFG (WHO), IGT	2421	57%	57.6	14	Stroke, CHD
Fisman, 2001 [91]	Israel	IFG (WHO)	11,853	18%	59.7	7.7	All-cause mortality, CVD mortality
George, 2015 [92]	United Kingdom	IGT	768	29%	65.4	3.9	All-cause mortality, CVD mortality, CVD events, CHD
Hajebrahimi, 2017 [93]	Iran	IFG (ADA), IGT	7249	54%	46.8	11.3	CVD events
Hermanides, 2019 [94]	Netherlands	HbA1c (ADA)	7900	38%	65.8	4.3	All-cause mortality
Hubbard, 2019 [95]	USA	IFG (ADA), HbA1c (ADA)	3313	63%	53.1	11.1	All-cause mortality, CVD events, CHD, Stroke, Heart Failure
Janszky, 2009 [96]	Sweden	IFG (ADA)	1167	30%	59.4	8	All-cause mortality, CVD mortality, Stroke, Heart Disease, Heart Failure
Jiang, 2020 [97]	China	IFG (ADA), IFG (WHO), IGT, HbA1c (ADA), HbA1c (IEC)	17939	73%	65.2	7.8	All-cause mortality, CVD mortality
Khang, 2010 [98]	South Korea	IFG (ADA)	9791	55%	43.2	5.8	CVD, Stroke, Heart Disease
Kim, 2019 [99]	South Korea	IFG (WHO), IGT, HbA1c (ADA)	7728	47.4%	52	9	CKD
Kowall, 2011 [100]	Germany	IFG (WHO), IGT	1,653	48%	64.1	10	All-cause mortality

Liu, 2018 [101]	China	IFG (ADA), IGT, HbA1c (ADA)	4193	28.2%	57.7	6.7	CVD events
Liu, 2007 [102]	China	IFG (ADA)	30,378	47%	46.4	10	CVD events, CHD, Stroke
Lu, 2019 [103]	China	IFG (ADA), IGT, HbA1c (ADA)	193,846	66%	56.6	3.8	All-cause mortality, CVD events
Ma, 2012 [104]	South Korea	IFG (ADA)	16,048	60%	55.7	9	CVD mortality
Michishita, 2017 [105]	Japan	IFG (WHO)	303	0%	52.2	6	CKD
Palmieri, 2006 [106]	Italy	IFG (WHO)	20447	63.6%	50.4	10.4	CHD
Parizadeh, 2019 [107]	Iran	IFG (ADA), IFG (WHO), IGT	6892	50%	46.67	12	All-cause mortality, Stroke, CHD, CKD
Pavlovic, 2019 [108]	Serbia	IFG (ADA), IGT	150	12%	57	2.1	All-cause mortality, CVD mortality
Robich, 2019 [109]	USA	HbA1c (ADA)	5415	23%	N/A	2.6	All-cause mortality
Rutten-Jacobs, 2014 [110]	Netherlands	IFG (ADA)	427	55%	40.3	10.1	CVD events, Stroke
Samaras, 2015 [111]	Australia	IFG (ADA)	945	54%	78.6	2	All-cause mortality, Heart Disease, Stroke
Stacey, 2019 [112]	USA	IFG (ADA), IGT	4355	62%	72.0	6	CHD
Tai, 2004 [113]	Singapore	IFG (ADA)	4723	49%	38.3	8	CHD
Thrainsdottir, 2005 [114]	Iceland	IFG (WHO), IGT	19381	52%	53.9	21.5	All-cause mortality, CHD
Nakagami, 2004 [115]	Japan, USA, Brazil, Fiji, Mauritius	IFG (WHO), IGT	6817	54%	51.4	5.0	All-cause mortality, CVD mortality
Vistisen, 2018 [116]	United Kingdom	IFG, (ADA), IFG (WHO), HbA1c (ADA), IGT, HbA1c (IEC)	5427	28%	61.5	11.5	CVD events
Wang, 2008 [117]	Finland	IFG (ADA), IFG (WHO), IGT	1910	64%	69.0	13.8	Stroke
Welsh, 2020 [118]	United Kingdom	HbA1c (IEC)	357833	56%	56.1	8.9	CVD events
Neves, 2020 [119]	USA	IFG (ADA) HbA1c (ADA)	3701	45.5%	58.2	7.5	All-cause mortality, CVD events, CKD
Kim, 2008 [120]	USA	IFG (ADA), IGT	2993	58%	44.8	10.4	All-cause mortality, CVD mortality
Brunner, 2010 [121]	United Kingdom	IFG (WHO)	6868	30%	49.5	11.3	CHD
Hunt, 2004 [122]	USA	IFG (WHO)	2941	57%	43.4	12.7	All-cause mortality
Farhan, 2019 [123]	USA	IFG (ADA), HbA1c (ADA)	697	23%	58.7	3.0	CVD events
Evans, 2015 [124]	United Kingdom	IFG (WHO), IGT	246884	57%	63.0	6.0	All-cause mortality, CVD mortality
Bjarnason, 2019 [125]	Iceland	IFG (ADA), IGT, HbA1c, ADA	372	24%	65.1	2.9	CVD events
Wang, 2007 [126]	Finland	IGT	1025	49%	65-74 years	13.5	CVD mortality
Ding, 2014 [127]	China	IFG (ADA)	1726	34%	64.0	3.1	All-cause mortality, CVD mortality

McNeill, 2006 [128]	USA	IFG (WHO)	3585	62%	72	11	CHD

Total sample size (after adjusting for overlapping cohorts) = 1,847,523

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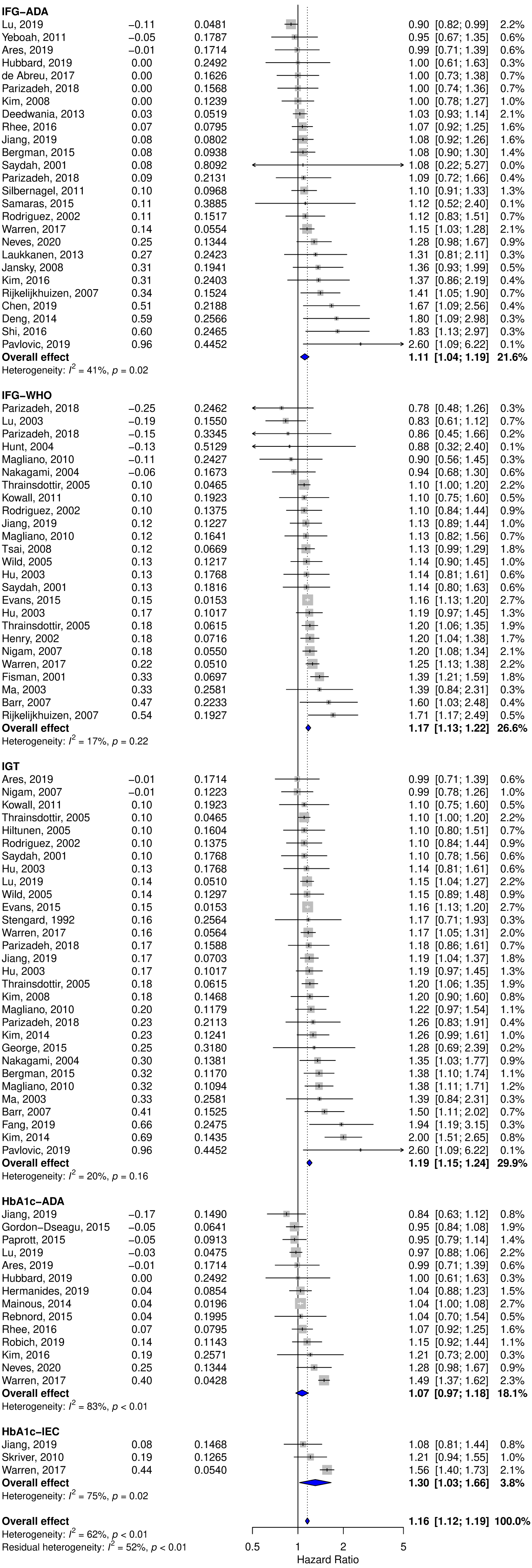
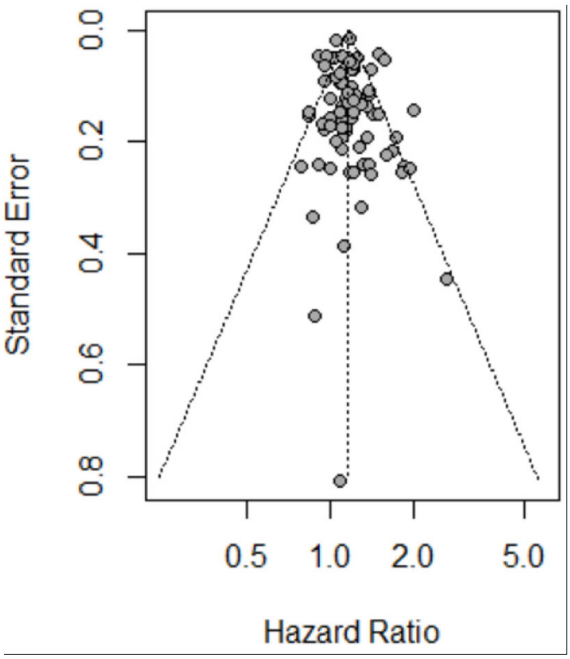
Supplemental Figure 2. All-Cause Mortality

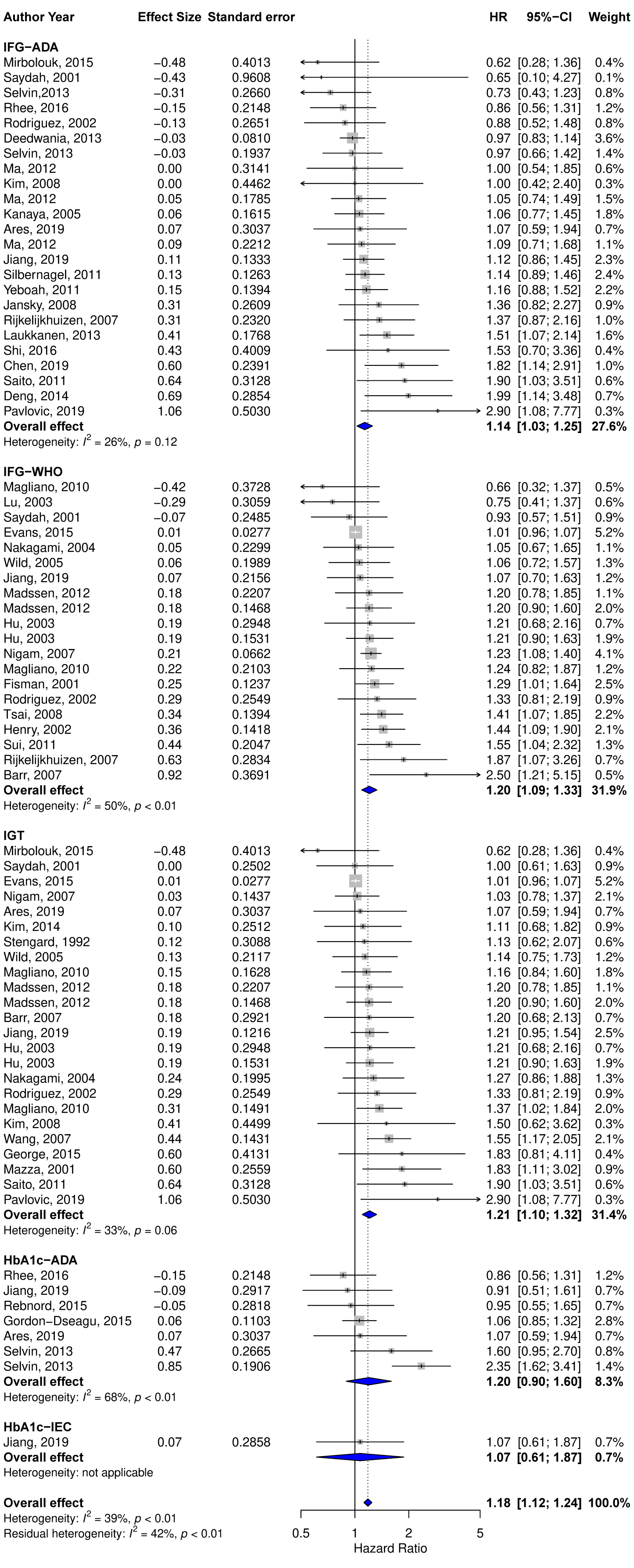


Supplemental Figure 9

Funnel Plot: All-cause Mortality



Supplemental Figure 3. Cardiovascular Disease Mortality



Supplemental Table 4. The association between intermediate hyperglycemia and all-cause mortality, cardiovascular disease mortality, cardiovascular disease, stroke, heart disease, heart failure, and chronic kidney disease by region and presence of a pre-existing condition

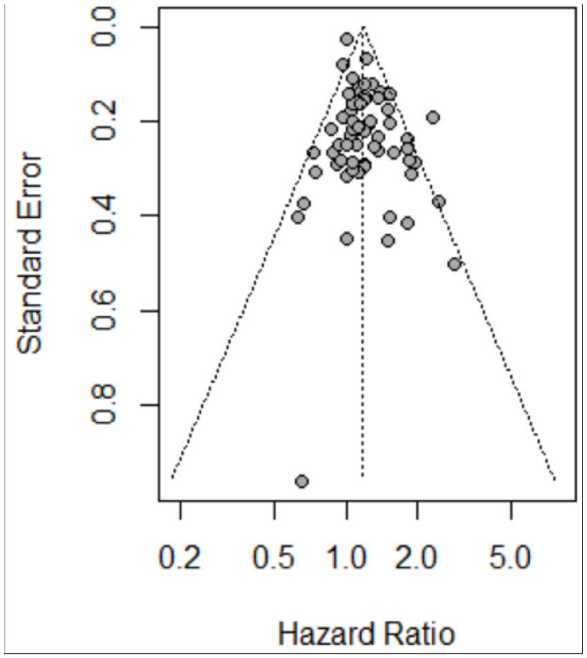
	IFG-ADA			IFG-WHO			IGT			HbA1c-ADA			HbA1c-IEC		
	No. of Studies	HR [95% CI]	P value	No. of Studies	HR [95% CI]	P value	No. of Studies	HR [95% CI]	P value	No. of Studies	HR [95% CI]	P value	No. of Studies	HR [95% CI]	P value
Mortality															
Region															
Europe	6	1.23 [1.04-1.44]	0.49	9	1.16 [1.13-1.19]	0.66	12	1.16 [1.13-1.19]	**0.05**	5	0.98 [0.90- 1.06]	0.22	1	1.21 [0.94-1.55]	**0.02**
USA/ Canada	8	1.08 [1.02-1.16]		6	1.16 [1.05-1.28]		5	1.14 [1.04-1.24]		5	1.20 [0.96-1.49]		1	1.56 [1.40-1.73]	
Asia	7	1.21 [1.01-1.45]		4	1.12 [1.01-1.24]		7	1.36 [1.17-1.57]		4	0.99 [0.92-1.07]		1	1.08 [0.81-1.44]	
Australia	2	1.02 [0.78- 1.36]		1	1.60 [1.03-2.48]		1	1.50 [1.11-2.02]		-	-		-	-	
Middle East	3	1.06 [0.92-1.23]		3	1.04 [0.67-1.61]		3	1.30 [1.10- 1.54]		-	-		-	-	
Africa	-	-		2	1.05 [0.81-1.37]		2	1.30 [1.11- 1.53]		-	-		-	-	
South America	-	-		-	-		-	-		-	-		-	-	
Pre-existing Cardiovascular Condition															
No	21	1.07 [1.01- 1.14]	**0.03**	24	1.16 [1.13- 1.19]	**0.01**	28	1.19 [1.14-1.23]	0.30	11	1.06 [0.95-1.19]	0.91	3	1.30 [1.03-1.66]	NA
Yes	5	1.45 [1.11- 1.88]		1	1.39 [1.21-1.59]		2	1.70 [0.86- 3.37]		3	1.0741 [0.95- 1.22]		0	NA	
CVD Mortality															
Region															
Europe	6	1.29 [1.10-1.52]	**0.01**	8	1.19 [1.03-1.37]	0.45	12	1.25 [1.08- 1.45]	0.53	3	1.05 [0.87-1.27]	**<0.01**	-	-	NA
USA/ Canada	8	0.99 [0.89-1.11]		5	1.20 [1.00-1.43]		4	1.10 [0.89-1.36]		2	2.03 [1.41-2.92]		1	1.07 [0.61-1.87]	
Asia	9	1.24 [1.03-1.50]		3	1.24 [1.01-1.53]		4	1.26 [1.05-1.50]		2	0.88 [0.63- 1.23]		-	-	
Australia				1	2.50 [1.21-5.15]		1	1.20 [0.68-2.13]		-	-		-	-	
Middle East	1	0.62 [0.28-1.36]		1	1.29 [1.01-1.64]		1	0.62 [0.28-1.36]		-	-		-	-	
Africa	-	-		2	0.98 [0.54-1.78]		2	1.27 [1.02-1.58]		-	-		-	-	
South America	-	-		-	-		-	-		-	-		-	-	
Pre-existing Cardiovascular Condition															
No	18	1.06 [0.97-1.16]	**0.04**	19	1.20 [1.08-1.33]	0.58	22	1.183 [1.09-1.29]	0.05	6	1.23 [0.89-1.71]	0.42	1	1.07 [0.61-1.87]	NA
Yes	6	1.40 [1.09-1.80]		1	1.29 [1.01-1.64]		2	2.20 [1.18-4.12]		1	0.95 [0.55-1.65]		-	-	
CVD Events															
Region															
Europe	7	1.22 [0.96-1.56]	0.28	3	1.11 [0.93-1.34]	0.21	8	1.23 [1.06-1.43]	0.53	9	1.12 [1.03-1.23]	0.20	4	1.16 [1.01-1.34]	**<0.01**
USA/ Canada	9	1.16 [1.01-1.33]		2	1.21 [1.07-1.37]		3	1.14 [1.02-1.28]		4	1.38 [1.07-1.79]		1	1.91 [1.65-2.21]	
Asia	7	1.07		3	1.60		6	1.17		3	1.04				

		[0.94-1.22]			[1.12-2.27]			[1.07- 1.27]			[0.89- 1.21]			
Australia	-	-		-	-		-	-		-	-		-	-	
Middle East	2	1.46 [1.05-2.05]					2	1.46 [1.05-2.05]							
Africa	1	1.77 [0.92-3.40]													
South America	-	-		-	-		-	-		-	-		-	-	
Pre-existing Cardiovascular Condition															
No	18	1.14 [1.04-1.26]	0.63	7	1.20 [1.08-1.32]	0.25	15	1.17 [1.09-1.24]	0.21	12	1.14 [1.00-1.31]	0.77	5	1.32 [1.00-1.73]	NA
Yes	8	1.22 [0.96-1.54]		1	1.86 [0.88-3.95]		4	1.33 [1.10-1.62]		4	1.18 [0.96-1.45]		-	-	
Stroke Events															
Region															
Europe	3	1.29 [0.99-1.69]	0.22	4	1.21 [1.05-1.40]	0.93	5	1.29 [1.07-1.56]	0.71	2	1.22 [0.72-2.08]	0.18	2	1.28 [0.72-2.27]	NA
USA/ Canada	7	0.94 [0.80-1.11]		1	1.13 [0.86-1.49]		1	1.17 [0.76- 1.81]		3	1.39 [1.15-1.66]				
Asia	4	1.10 [0.90-1.36]		2	0.99 [0.22-4.34]		4	1.26 [0.80-1.98]		1	1.22 [0.72; 2.08]				
Australia															
Middle East	3	1.29 [0.86-1.93]		2	1.47 [0.59-3.63]		3	0.91 [0.51-1.62]							
Africa	1	1.49 [0.59-3.75]													
South America															
Pre-existing Cardiovascular Condition															
No	15	1.06 [0.95-1.19]	0.87	9	1.22 [1.07- 1.40]	NA	13	1.24 [1.06-1.45]	NA	6	1.23 [1.04-1.46]	NA	2	1.28 [0.72-2.27]	NA
Yes	3	1.03 [0.71- 1.49]		-			-	1		-	-		-	-	
Heart Disease Events															
Region															
Europe	1	1.12 [0.80-1.57]	0.86	6	1.19 [1.03-1.21]	0.16	5	1.12 [1.03-1.22]	0.18	2	1.12 [0.95-1.33]	**0.05**	2	1.33 [0.74-2.38]	NA
USA/ Canada	6	1.10 [0.99-1.21]		1	1.45 [1.15-1.83]		2	0.96 [0.79-1.17]		3	1.47 [1.27-1.70]		-	-	
Asia	7	1.19 [1.00-1.41]		3	0.97 [0.62-1.52]		6	1.32 [1.07-1.63]		1	1.24 [0.97-1.60]		-	-	
Australia	-	-		-	-		-	-		-	-		-	-	
Middle East	3	1.02 [0.72-1.46]		3	1.0500 [0.8048; 1.3699]		3	1.2346 [0.8307; 1.8349]		-	-		-	-	
Africa	1	0.96 [0.62-1.48]		-	-		-	-		-	-		-	-	
South America	-	-		-	-		-	-		-	-		-	-	
Pre-existing Cardiovascular Condition															
No	16	1.11 [1.01-1.21]	0.94	13	1.14 [1.06-1.22]	NA	15	1.13 [1.06-1.21]	0.85	6	1.28 [1.13-1.46]	NA	2	1.33 [0.74-2.38]	NA
Yes	2	1.10 [0.92-1.30]		-	-		1	1.19 [0.69- 2.06]		-	-		-	-	
Heart Failure Events															

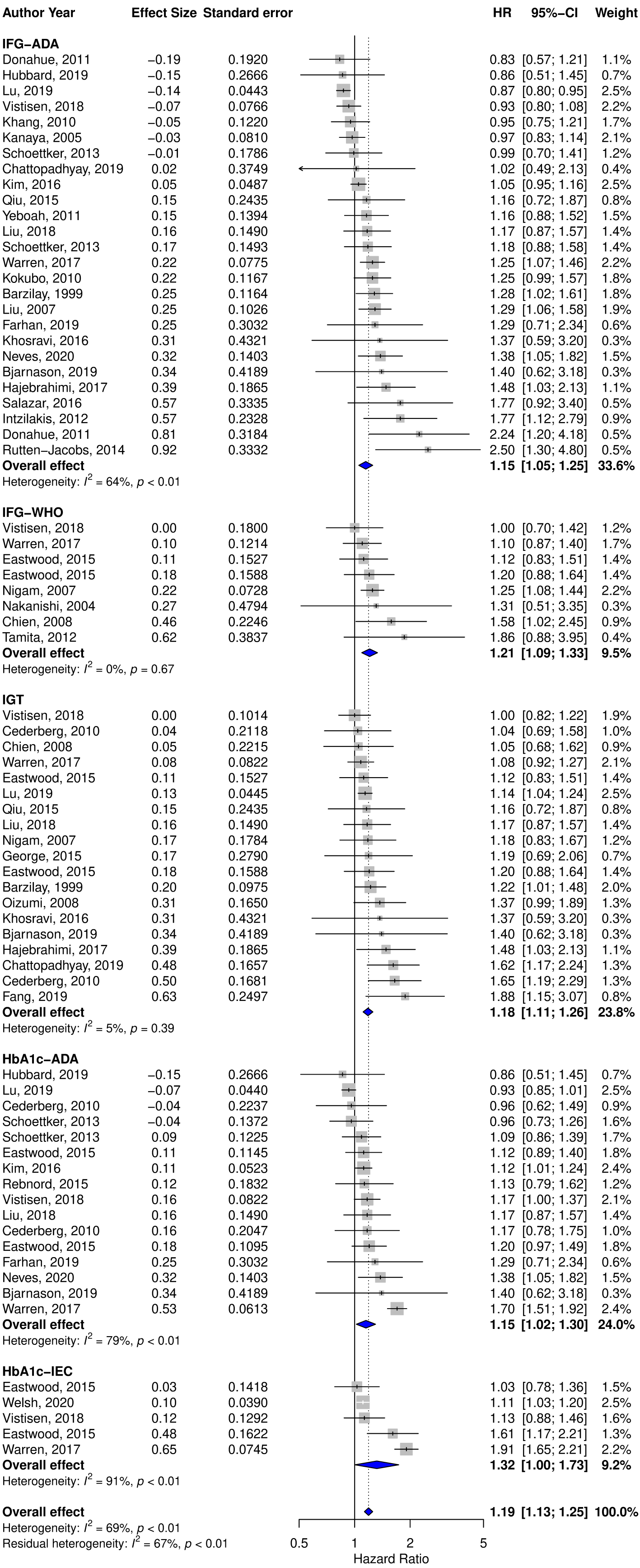
Region														
Europe	1	1.13 [0.82-1.54]	0.25	-	-	NA	-	-	NA	-	-	NA	-	-	NA
USA/ Canada	4	0.92 [0.81-1.05]		-	-		1	5.04 [1.00-25.40]		3	1.13 [0.87-1.45]		-	-	
Asia	-	-		-	-		-	-		-	-		-	-	
Australia	-	-		-	-		-	-		-	-		-	-	
Middle East	-	-		-	-		-	-		-	-		-	-	
Africa	-	-		-	-		-	-		-	-		-	-	
South America	-	-		-	-		-	-		-	-		-	-	
Pre-existing Cardiovascular Conditions															
No	4	0.92 [0.81-1.05]	0.25	-	-	NA	1	5.04 [1.00-25.40]	NA	3	1.13 [0.87-1.45]	NA	-	-	NA
Yes	1	1.13 [0.82-1.55]		-	-		-	-		-	-		-	-	
CKD Events															
Region			0.82			**0.04**			0.26			0.53			NA
Europe	-	-		-	-		-	-		-	-		-	-	
USA/ Canada	3	1.09 [1.00-1.19]		1	1.28 [1.14-1.43]		2	1.14 [1.02-1.28]		2	1.28 [1.02-1.60]		1	1.50 [1.32-1.70]	
Asia	-	-		3	1.07 [0.83-1.38]		2	1.40 [0.93-2.11]		1	1.39 [1.21-1.60]		-	-	
Australia	-	-		-	-		-	-		-	-		-	-	
Middle East	2	1.12 [0.89-1.41]		2	0.91 [0.71-1.17]		2	0.94 [0.71-1.25]		-	-		-	-	
Africa	-	-		-	-		-	-		-	-		-	-	
South America	-	-		-	-		-	-		-	-		-	-	

Supplemental Figure 10

Funnel Plot: Cardiovascular Mortality

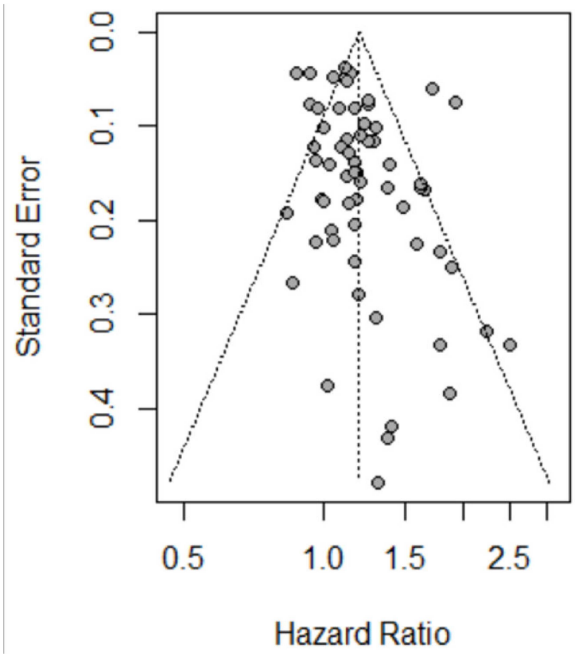


Supplemental Figure 4. Cardiovascular Events

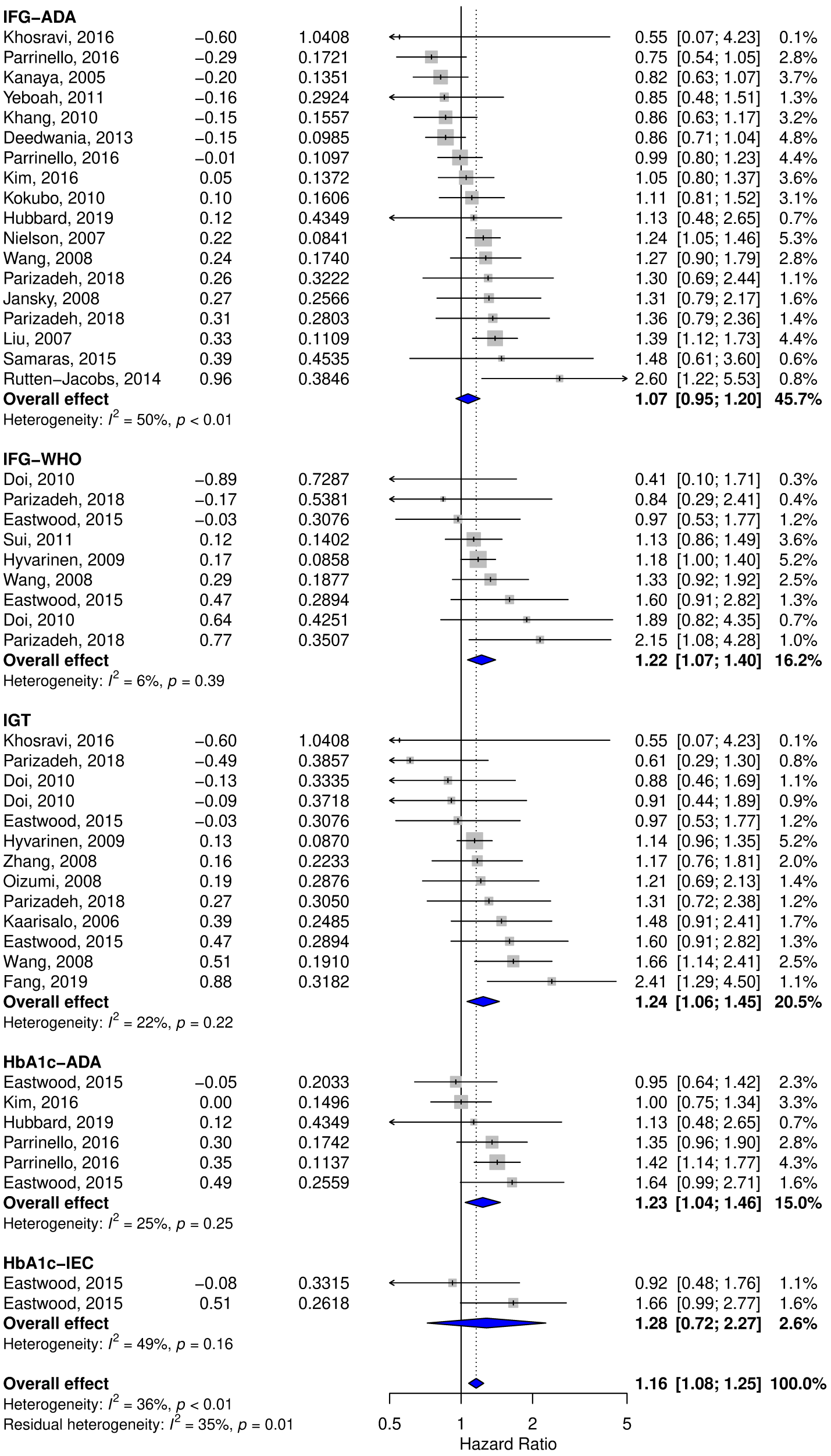


Supplemental Figure 11

Funnel Plot: Cardiovascular Events

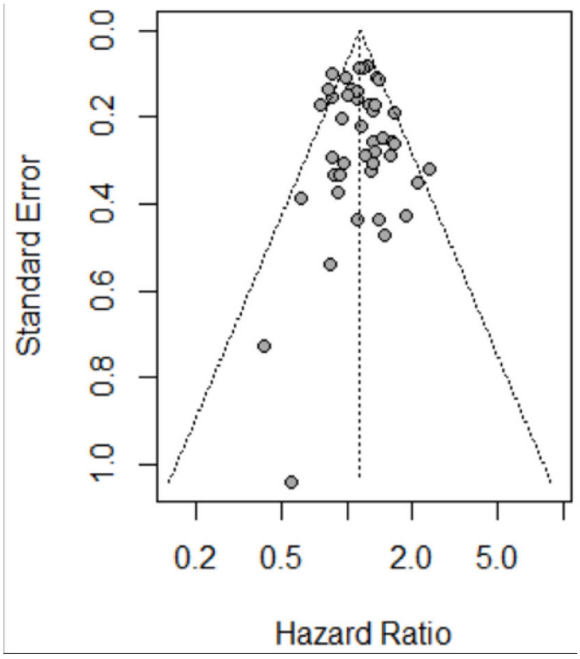


Supplemental Figure 5. Stroke Events

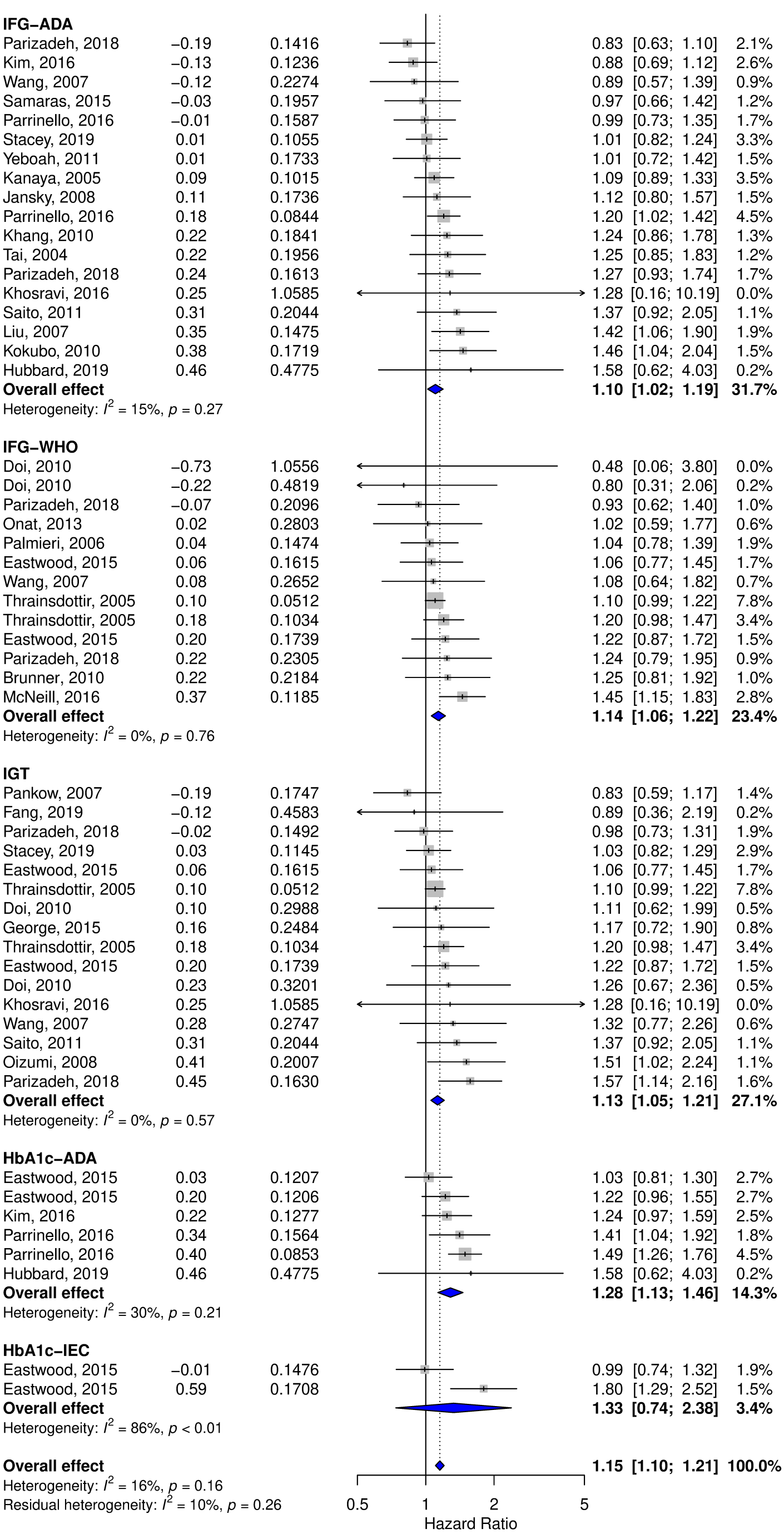


Supplemental Figure 12

Funnel Plot: Stroke Events

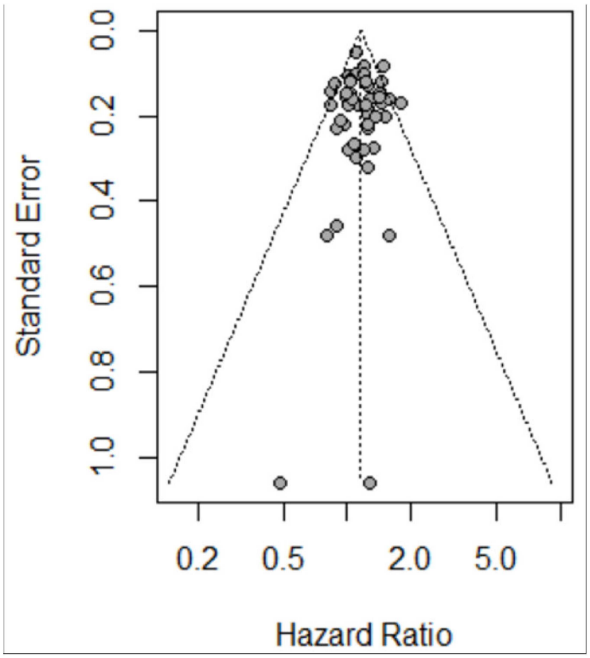


Supplemental Figure 6. Heart Disease Events

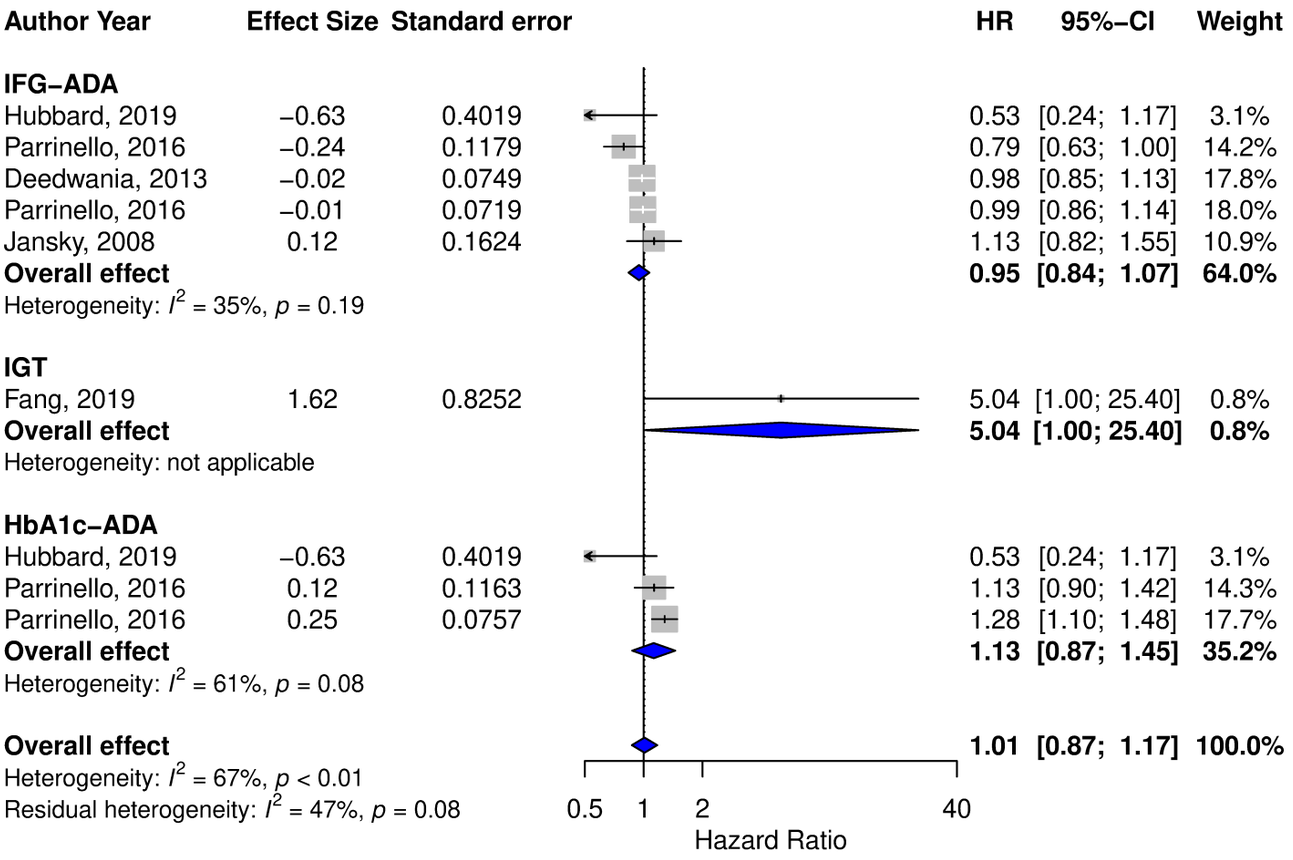


Supplemental Figure 13

Funnel Plot: Heart Disease Events

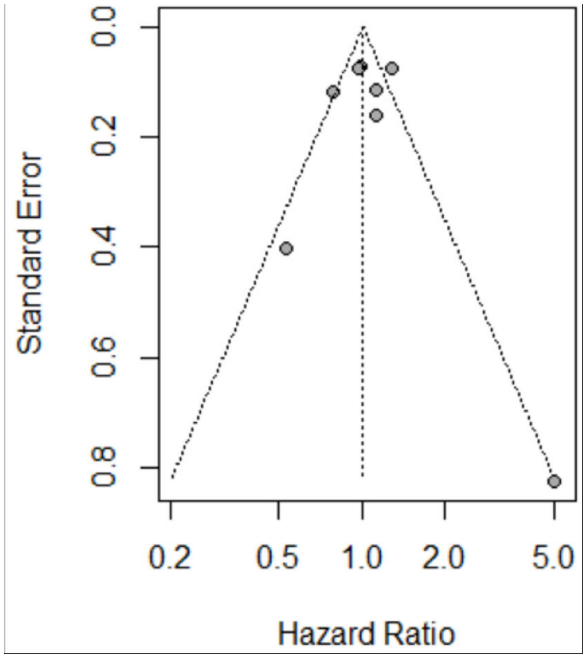


Supplemental Figure 7. Heart Failure Events

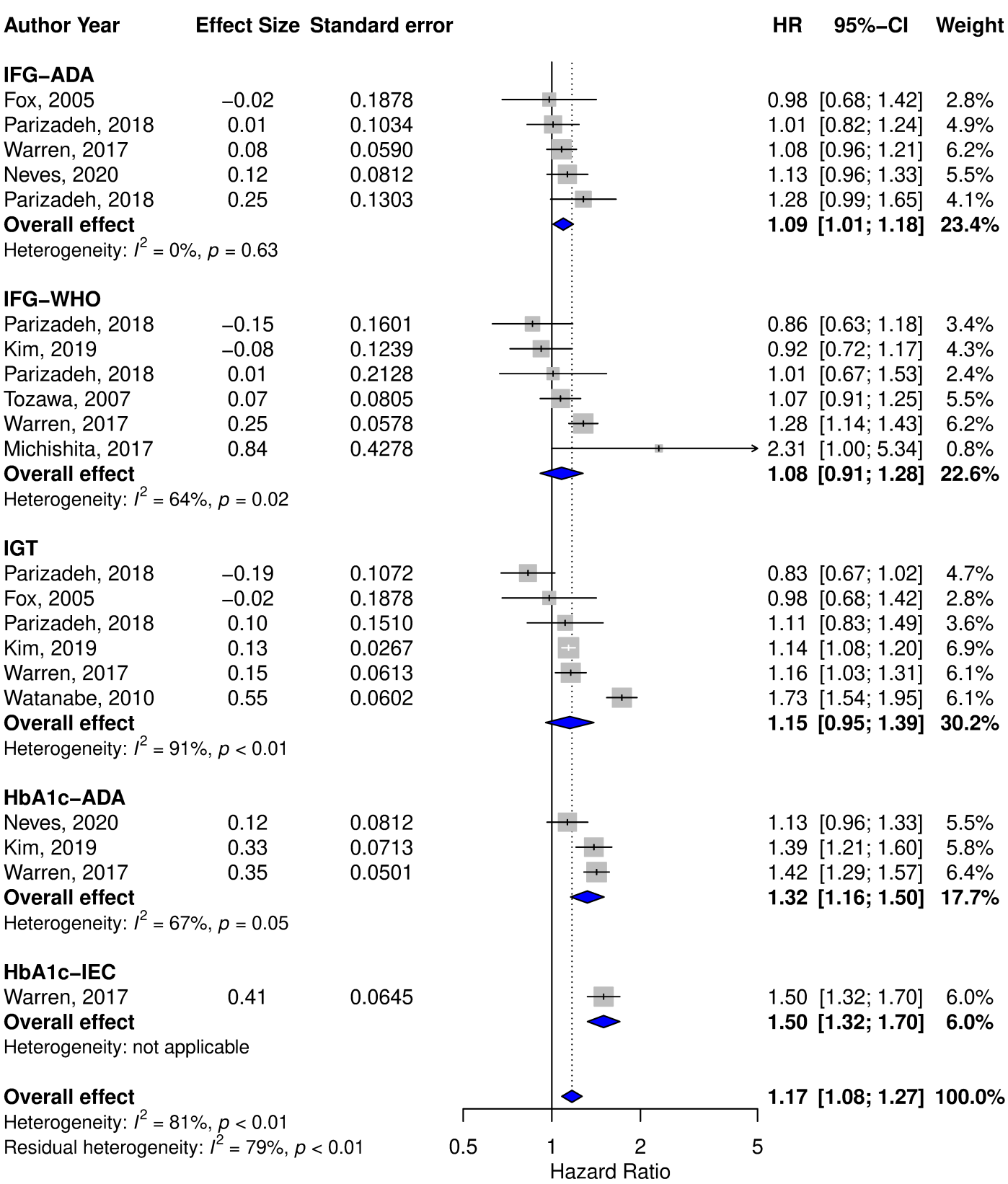


Supplemental Figure 14

Funnel Plot: Heart Failure Events



Supplemental Figure 8. Chronic Kidney Disease



Supplemental Figure 15

Funnel Plot: Chronic Kidney Disease Events