Does type 2 diabetes confer higher relative rates of cardiovascular events in women compared with men?

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Aims
To investigate whether diabetes confers higher relative rates of cardiovascular events in women compared with men using contemporary data, and whether these sex-differences depend on age.

Methods and results
All Danish residents aged 40–89 years without a history major adverse cardiovascular events, including heart failure, as of 1 January 2012 until 31 December 2016 were categorized by diabetes-status and characterized by individual-level linkage of Danish nationwide administrative registers. We used Poisson regression to calculate overall and age-dependent incidence rates, incidence rate ratios, and women-to-men ratios for myocardial infarction, heart failure, ischaemic stroke, or cardiovascular death (MACE-HF). Among 218,549 (46% women) individuals with diabetes, the absolute rate of MACE-HF was higher in men than in women (24.9 vs. 19.9 per 1000 person-years). Corresponding absolute rates in men and women without diabetes were 10.1 vs. 7.0 per 1000 person-years. Comparing individuals with and without diabetes, women had higher relative rates of MACE-HF than men [2.8 (confidence interval, CI 2.9–2.9) in women vs. 2.5 (CI 2.4–2.5) in men] with a women-to-men ratio of 1.15 (CI 1.11–1.19, \( P < 0.001 \)). The relative rates of MACE-HF were highest in the youngest and decreased with advancing age for both men and women, but the relative rates were higher in women across all ages, with the highest women-to-men ratio between age 50 and 60 years.

Conclusion
Although men have higher absolute rates of cardiovascular complications, the relative rates of cardiovascular complications associated with diabetes are higher in women than in men across all ages in the modern era.

Keywords
Cardiovascular disease • Diabetes

Introduction
Type 2 diabetes (diabetes) and male sex are well-established risk factors for the development of cardiovascular disease (CVD), but several studies have shown that the impact of diabetes on CVD may be greater in women than in men. Older studies have predominantly observed that women have excess rates of coronary heart disease, heart failure, stroke, CVD-related death, and all-cause mortality.
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Methods

Data sources

All residents in Denmark receive a unique and permanent civil registration number at birth or immigration that enables individual-level linkage between nationwide registries. Data for this study were obtained from: (i) the Danish Civil Registration System registry (sex, date of birth, immigration, emigration, and vital status), (ii) the Danish National Patient Registry (discharge diagnoses coded according to the International Classification of Diseases (ICD)-8 since 1977, and ICD-10 system since 1994), (iii) the Danish National Prescription Registry (claimed prescriptions since 1995 according to the Anatomical Therapeutic Classification (ATC)), and (iv) the Danish National Causes of Death Registry (primary and underlying causes of death from death certificates). All registries have been validated previously. We excluded individuals with type 1 diabetes, defined as monotherapy with insulin (ATC = A10A) before age 30 years. If the only drug dispensations were metformin (ATC = A10BA02) in women <40 years of age, the individual was considered to have possible polycystic ovary syndrome, and these dispensations were not counted. Thus, claimed prescriptions after age 40 years for women with a diagnosis of possible polycystic ovary syndrome were considered as diabetes medications and lead to inclusion at the first date of purchase after the 40th birthday. For women without diabetes prior to pregnancy [42 weeks prior to giving birth (ICD-10 codes O80–O84)], who claimed a prescription for insulin between 42 weeks prior to and 30 days after giving birth were considered as having gestational diabetes, and dispensations of glucose-lowering medication during and in relation to pregnancy were not considered. We excluded patients with a diagnosis of coronary artery disease, heart failure, or ischaemic stroke prior to study entry, as well as individuals who immigrated to Denmark after 1 January 2012.

Outcomes

The primary outcome was MACE-HF, comprising the composite of first-time myocardial infarction, heart failure, ischaemic stroke, or cardiovascular death (ICD-10-codes in Supplementary material online, Table S1), whichever came first. The secondary outcomes were first and second occurrence of myocardial infarction, heart failure, ischaemic stroke, and all-cause mortality. A grace period of 30 days was used for recurrent outcomes, thus a recurrent outcome could only be classified as a recurrent outcome 30 days following the first-time event. The diagnoses for the first-time endpoints have been validated in Danish registers with high positive predictive value, i.e. 97% (men 97%, women 97%) for myocardial infarction, 83.6% (men 85.4%, women 81.5%) for heart failure, and 97% for ischaemic stroke. The definition of ischaemic stroke included diagnoses of ischaemic stroke and unspecified stroke, as the majority of unspecified strokes in prior validation studies were of ischaemic origin. Discharge diagnoses for recurrent events have been validated with lower positive predictive values, i.e. 88% (men 88%, women 87%) for myocardial infarction and 66% for heart failure, with no validity on recurrent ischaemic stroke.

Statistics

All individuals were followed from the date of entry until either the first-time event of interest, death, emigration, age 90 years or 31 December 2016, whichever came first. For recurrent events, all individuals alive 30 days after the first-time event were followed from that day until either the recurrent event, death, emigration, age 90 years or 31 December 2016, whichever came first.

We present population characteristics on 1 January 2012 as medians with interquartile ranges for continuous variables, and as counts with percentages for categorical variables. We use Poisson regression to calculate overall and age-dependent incidence rates (IRs), rate ratios (IRR), and women-to-men ratios (WMR). We report incidence rates (IR = events/1000 person-years), incidence rate ratios (IRR = IR_disease/IR_nondisease), and women-to-men ratios (WMR = IR_women/IR_men) with 95% confidence intervals (CIs). In age-dependent Poisson regression, age (40–89 years of age) is divided in 1-year bands and updated consecutively throughout the study period, allowing to study a non-linear age effect using thin plate splines. We calculate a two-sided P-value for the overall WMRs. We set the significance level to 5%.
In secondary analyses, we repeat all analyses with first-time myocardial infarction, first-time heart failure, first-time ischaemic stroke, and all-cause mortality as outcome, and age-dependent analyses on recurrent myocardial infarction, heart failure, and ischaemic stroke in the subgroup of patients with a first-time event, respectively.

We conduct an age-dependent sensitivity analysis for first-time MACE-HF, excluding individuals with a diagnosis of diabetes and a diagnosis of MACE-HF on the same day. We further conduct sensitivity analyses on first-time MACE-HF and ischaemic stroke, in which age-dependent analyses are stratified by status of atrial fibrillation, excluding individuals with a diagnosis of atrial fibrillation and an event of interest on the same day. All statistical analyses were conducted using R.

**Ethics**

Retrospective register studies do not need ethical approval in Denmark. The Danish Data Protection Agency has approved the project (reference number 2007-58-015/GEH 2014-014, I-Suite no: 02734).

**Results**

The study included 148 385 (47% women) individuals with prevalent diabetes on 1 January 2012 (Table 1), 66 078 individuals (46% women) with incident diabetes between 2012 and 2017, and 4086 individuals with diabetes irrespective of diabetes status (comorbidities than those without diabetes, but that the comorbidities and treated comorbidities were somewhat similar between men and women irrespective of diabetes-status (Table 1).

**Incidence rates**

During above 13 million person-years of follow-up, 121 745 new-onset MACE-HF events were identified (Table 2), consisting of 30 884 myocardial infarctions, 27 731 heart failures, 40 938 ischaemic strokes, and 37 096 CVD deaths. There were 7744 MACE-HF events in women with diabetes over 389 thousand person-years of follow-up, equal to an IR of 19.9/1000 person-years (Figure 1). Population characteristics in 1 January 2012 showed that individuals with diabetes had higher levels of comorbidities and treated comorbidities than those without diabetes, but that the comorbidities and treated comorbidities were somewhat similar between men and women irrespective of diabetes-status (Table 1).

**Age-specific incidence rates**

The IRs of MACE-HF and all secondary outcomes increased with advancing age and were higher in men than in women irrespective of diabetes-status and age (Figure 2A, Supplementary material online, Figures S3–S6A). Regardless of diabetes-status and outcome, women were older than men at time of event with myocardial infarction presenting at the lowest median age (74.4 for women with diabetes, 68.4 for men with diabetes) and heart failure (76.8 for women with diabetes, 71.2 for men with diabetes) and all-cause death at the highest (77.1 for women with diabetes, 73.2 for men with diabetes; Table 2, Supplementary material online, Tables S2A–S2D).

The sex-specific relative rates (diabetes:no diabetes) for all outcomes were highest in the youngest individuals and decreased with advancing age (Figure 2B, Supplementary material online, Figures S3–S6B). The IRRs for MACE-HF were higher in women than in men at all ages, with the highest women-to-men ratio between age 50 and 60 years (Figure 2C), although insignificant from age < 45 years. Somewhat similar findings were evident for all secondary outcomes, although not in the young for ischaemic stroke (age < 45 years) in which men had higher relative rates compared with women (Supplementary material online, Figures S3–S6). Excluding events on the same day as the diagnosis of diabetes did not change the results (Supplementary material online, Figures S7–S11).

In individuals without atrial fibrillation, the women-to-men-ratio for MACE-HF and ischaemic stroke were largely unchanged. In individuals with atrial fibrillation, we identified 33 513 events of MACE-HF and 9736 events of ischaemic stroke with a risk-time of 62 000 and 65 000 person-years, respectively (Supplementary material online, Table S4A and B), and we confirmed the findings for MACE-HF, whereas we observed no sex difference in IRRs of ischaemic stroke in individuals with atrial fibrillation across all ages (Supplementary material online, Figures S12 and S13).

During the 30-day grace period for analyses of recurrent events, patients were largely excluded due to death, with the highest mortality among patients with diabetes and the elderly, whereas men and women had a largely comparable mortality across age-groups regardless of diabetes-status (Supplementary material online, Tables S5A–S5C). Irrespective of diabetes, the IRRs of recurrent myocardial infarction, heart failure, and ischaemic stroke generally increased with advancing age in men and women (Supplementary material online, Figures S14–S16A). We observed comparable IRs as well as IRRs in women and men for all recurrent events across all ages and irrespective of diabetes status, except for recurrent myocardial infarction in subgroups of men. In men with diabetes above age 55 years, the IRRs of recurrent myocardial infarction were higher than in men without diabetes, and in individuals older than age 75 years, we observed higher IRRs of recurrent myocardial infarction in men than in women (Supplementary material online, Figures S14–S16B and C).

**Discussion**

In this nationwide study, we observed that although men have higher rates of first-time cardiovascular complications, the relative rate of first-time cardiovascular complications associated with diabetes are higher in women than in men across all ages in the modern era. However, in recurrent events these sex-differences in the relative rate of cardiovascular complications were no longer present.

These results are similar to a study using recent data, which reported a non-significantly higher relative rate of first-time MACE.
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Table 1  Population characteristics in 1 January 2012

|                        | Women                        | Men                        |
|------------------------|------------------------------|----------------------------|
|                        | No diabetes (N = 1 266 291)  | Diabetes (N = 69 057)      |
| Age, median (IQR)      | 57.3 (48.1–67.3)             | 65.4 (56.1–73.7)           |
| Comorbidity (%)        |                              |                            |
| Atrial fibrillation    | 23 380 (1.9)                 | 2998 (4.3)                 |
| Chronic renal failure  | 4815 (0.4)                   | 1116 (1.6)                 |
| COPD                   | 34 610 (2.7)                 | 3 942 (5.7)                |
| Dyslipidaemia          | 201 645 (15.9)               | 51 255 (74.2)              |
| Hypertension           | 189 761 (15.0)               | 32 948 (47.7)              |
| Diabetes duration, years (%) |                       |                            |
| <5                     | —                            | 31 873 (46.2)              |
| 5–10                   | —                            | 17 469 (25.3)              |
| 10–15                  | —                            | 9984 (14.5)                |
| >15                    | —                            | 9731 (14.1)                |
| Highest attained education (%) |                   |                            |
| Basic school           | 385 199 (30.4)               | 33 419 (48.4)              |
| High school            | 45 917 (3.6)                 | 1647 (2.4)                 |
| Vocational education   | 438 464 (34.6)               | 21 109 (30.6)              |
| Short/medium length higher education |            | 9021 (13.1)               |
| Long higher education, research | 70 318 (5.6)            | 1528 (2.2)                 |
| Unknown                | 30 942 (2.4)                 | 2333 (3.6)                 |
| Ethnicity (%)          |                              |                            |
| Danish                 | 1 173 585 (92.7)             | 60 738 (88.0)              |
| Immigrants             | 90 555 (7.2)                 | 8234 (11.9)                |
| Offspring of first-generation immigrants | 2137 (0.2)         | 85 (0.1)                   |
| Medicine (%)           |                              |                            |
| Antidiabetics          |                              |                            |
| Metformin              | —                            | 44 787 (64.9)              |
| Insulin                | —                            | 15 711 (22.8)              |
| Sulfonylureas          | —                            | 12 902 (18.7)              |
| GLP1-analogues         | —                            | 4456 (6.5)                 |
| DPP4-inhibitors        | —                            | 3128 (4.5)                 |
| Anticoagulants         |                              |                            |
| Aspirin                | 78 235 (6.2)                 | 20 089 (29.1)              |
| ADP-receptor inhibitors| 82 326 (6.5)                 | 20 555 (29.8)              |
| Vitamin K-antagonists  | 15 122 (1.2)                 | 2194 (3.2)                 |
| NOAC                   | 2691 (0.2)                   | 234 (0.3)                  |
| Other                  |                              |                            |
| Beta-blockers          | 96 292 (7.6)                 | 13 183 (19.1)              |
| Calcium channel blockers | 111 520 (8.8)         | 18 281 (26.5)              |
| RASi                   | 198 103 (15.6)               | 39 503 (57.2)              |
| Statins                | 151 668 (12.0)               | 41 897 (60.7)              |

ADP, adenosine diphosphate; COPD, chronic obstructive pulmonary disease; DPP4, dipeptidyl peptidase 4; GLP1, glucagon-like peptide 1; IQR, interquartile range; NOAC, novel oral anticoagulant; RASi, renin–angiotensin system inhibitors.

*aData missing for 56 individuals.

(without heart failure), myocardial infarction, and stroke associated with diabetes in women compared with men, but only patients with newly diagnosed diabetes were included limiting comparisons between the studies. Interestingly, while their association in relative rates were attenuated in both sexes from the unadjusted to the fully adjusted model, their results in WMRs remained unchanged, indicating that the relation of relative ratios between sexes may not be affected majorly by these potential confounders. Furthermore, conflicting findings from other studies using data from the past two decades are evident, as some studies have observed a significant excess...
rate in women regarding coronary heart disease, heart failure, death from coronary heart disease, and all-cause death associated with diabetes, while others observed no differences between sexes for heart failure, stroke, death from myocardial infarction, and all-cause mortality. Although most of these studies were large, our study had sufficient power to study sex-differences in all ages, including sufficient events in the young, and observed that women had a higher relative rate of MACE-HF and all secondary outcomes across all ages compared with men, although not at age < 45 years for ischaemic stroke.

Most studies investigating how sex-differences in the relative impact of diabetes on cardiovascular complications and mortality vary with age have used wide age-groups, thus not illustrating the full age effect. A recent study found that the WMRs for cardiovascular complications were age-dependent, with higher relative rates for coronary heart disease, stroke, and heart failure in women among younger individuals, with no difference in relative rates from age > 75 years, but age at diagnosis among newly diagnosed diabetes were included limiting the comparison with our study. In contrast to this and other studies, we observed WMRs to peak in the middle-aged (age 50–59 years) with lower WMRs at young and old age for MACE-HF, ischaemic stroke, and all-cause mortality. It is uncertain why, but all outcomes are rare in young individuals, especially in women, who generally experience their cardiovascular event and death later than men, thus the increased cardiovascular rate associated with diabetes may not yet have become apparent in young women. Furthermore, the level of hypertension is known to increase at a faster pace with advancing age, especially after menopause. However, both arguments are in contrast with our results for myocardial infarction and heart failure for which the highest WMRs were observed at youngest age and decreased with advancing age.

Older studies have observed higher relative rates of recurrent myocardial infarction and stroke associated with diabetes,
although none of them showed an age-effect. Contrarily, we observed broadly comparable rates of all recurrent events between patients with and without diabetes across all ages, with the exception of recurrent myocardial infarction in men, in which rates were significantly higher from age > 55 years in diabetic men compared with non-diabetic men. Our study cannot address why we observed a reduced impact of diabetes on recurrent cardiovascular outcomes compared with prior studies, but may be secondary to improvements in risk factor management in patients with diabetes and cardiovascular complications.5 Two of the prior studies stratified their analyses by sex and found higher relative rates of recurrent myocardial infarction in women compared with men.23,24 Conversely, we observed higher relative rates of myocardial infarction in men from age > 75 years compared with women, and no difference in relative rates of recurrent discharge of heart failure and ischaemic stroke across all ages between men and women.

Diabetes may confer higher relative rates of first-time cardiovascular complications in women because of interaction with sex hormones, since diabetes appears to attenuate the protective effect of oestrogen regarding atherosclerosis,26 as supported by the declining WMR of first-time events with advancing age as observed in our results. Other explanations could be differences in the cardiovascular risk factor burden, sex-differences in the healthcare provided for the prevention, management and treatment of diabetes and its complications (e.g. worse glycaemic control in women),27 or women being less adherent to guideline-recommended treatment.28 Given the lower absolute rate of CVD in women than in men, these findings may merely be explained by a comparable rate difference that leads to higher relative rates in women. It is unknown why these sex-differences appeared to diminish for recurrent events, but potentially secondary prophylaxis in patients with established cardiovascular complications attenuates the observed sex-differences, men and women are more equal regarding recurrent CVD events associated with diabetes in individuals with established CVD, or our population with first-time events was too small to detect statistically significant sex-differences.

**Strengths and limitations**

The major strengths of this nationwide study include minimal risk of selection bias, minimal loss to follow-up ensured by the comprehensive Danish registries and the large sample size with more than 13 million person-years. This enabled us to study sex-differences in associations between diabetes on cardiovascular events and mortality with sufficient power in all ages following the introduction of the new diabetes definition in Denmark at 1 January 2012 over a relatively short study period, but important limitations need to be addressed.

The primary limitation to this study is that our results rely on discharge diagnoses of myocardial infarction, heart failure, ischaemic stroke, and cardiovascular death reported in the medical charts at the hospitals and not on clinical data,29 but potential minor misclassifications are non-systematic and do not influence the overall validity of the data.13 Although the diagnoses of diabetes, myocardial infarction, and ischaemic stroke have high positive predictive values, and myocardial infarction a high sensitivity,29 PPVs by sex for diabetes and ischaemic stroke are unknown, and recurrent outcomes are validated with relatively lower PPVs. An older study revealed a high PPV and specificity, but a low sensitivity for the heart failure diagnosis of 29%,30 which should be acknowledged in the interpretation of the results. Furthermore, we cannot rule out that the true rates of diabetes, particularly all diet-treated cases, and cardiovascular events may have been underestimated, which may have biased our results. However, despite these limitations, our results generally concur with previous studies exploring sex-differences in the relative impact of diabetes on CVD and mortality.

Secondly, we did not have access to information on metabolic control (glucose-levels, lipids, and blood pressure), imaging
(echocardiography including measures of diastolic function), or lifestyle factors (smoking, alcohol consumption, body mass index, physical activity level, or diet).

Thirdly, since the majority of diagnoses of gestational diabetes and polycystic ovary syndrome are diagnosed in private practice, we used prescribed antidiabetics to define both diagnoses, which have not been validated. Our definitions capture women with gestational diabetes treated with insulin during pregnancy along with women with polycystic ovary syndrome treated with metformin. Although this also excluded women in monotherapy of metformin age < 40 years due to a diagnosis of diabetes from the diabetes exposure-time, these women would re-enter from age 40 years if still claiming prescriptions for antidiabetic medication. Women with polycystic ovary syndrome treated with metformin age > 40 years were not accounted for, thus may have contributed with risk time without many events, as polycystic ovary syndrome is not as strongly associated with CVD.
as diabetes. However, this is considered to be a minor group of women, thus it unlikely affected our results significantly.

Lastly, the majority of the Danish population is Caucasian, and we did not include individuals immigrating to Denmark during our study period due to unknown medical history, thus our results may not be generalizable to non-Caucasian people.

Conclusions

In this nationwide study, we observed that although men have higher absolute rates of first-time cardiovascular complications, the relative rate of first-time cardiovascular complications are higher in women than in men across all ages in the modern era. Secondly, these sex-differences are not present in recurrent cardiovascular outcomes. Further studies are warranted to more clearly elucidate the mechanisms responsible for the substantial sex-differences in diabetes-related first-time cardiovascular complications.

Supplementary material

Supplementary material is available at European Heart Journal online.

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References

1. The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215–2222.
2. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974;34:29–34.
3. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA 1979;241:2035–2038.
4. Prospective Studies Collaboration and Asia Pacific Cohort Studies Collaboration. Sex-specific relevance of diabetes to occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980793 adults from 68 prospective studies. Lancet Diabetes Endocrinol 2018;6:538–546.
5. Rawshani A, Rawshani A, Franzen S, Eliasson B, Svensson A-M, Miftaraj M, McGuire DK, Sattar N, Rosengren A, Gudbjornsdottir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med 2017;376:1407–1418.
6. Shah AD, Langenberg C, Rapsomaniki E, Demer DL, Clarke R, Collins R, Peto R, Udd L, Chen Z. Association between diabetes and cause-specific mortality in rural and urban areas of China. JAMA 2017;317:280–289.
7. Alegre-Díaz J, Herttington W, López-Cervantes M, Glaucic L, Ramirez R, Hill M, Bajent C, McCarthy ML, Lewington S, Collins R, Whislock G, Tapi-Conyer R, Peto R, Kuri-Morales P, Emberson J, Diabetic and cause-specific mortality in Mexico City. N Engl J Med 2016;375:1961–1971.
8. Lyne E, Sandegaard JL, Rebsom M. The Danish National Patient Register. Scand J Public Health 2011;39:30–33.
9. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39:38–41.
10. Carstensen B, Kristensen JK, Mccrussen MM, Borch-Johnsen K. The National Diabetes Registry. Scan J Public Health 2011;39:58–61.
11. Olesen JB, Lip GYH, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen A-M, Gislason GH, Torg-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:d124.
12. Sundbøll J, Adelborg K, Munch T, Fleslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. BMJ Open 2016;6:e012832.
13. Delektu J, Hansen SM, Alzuhair KS, Bork CS, Joensen AM. The validity of the diagnosis of heart failure (ISO-10509) in the Danish National Patient Register. Dan Med J 2018;65: https://ugetkrft.dk/dmj/validity-diagnosis-heart-failure-ISO-10509-danish-national-patient-register.
14. Kraup L-H, Boysen G, Janhua H, Prescott E, Truelsen T. Stroke subtype and cause of stroke in a National Register of Patients. Neuroepidemiology 2007;28:150–154.
15. Wood SN. Thin plate regression splines. J R Stat Soc Ser B Stat Methodol 2003;65:95–114.
16. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pas P, Vargas J, Lisheng L. INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet Lond Engl 2004;364:937–952.
17. Deeks JJ, Altman DG, Egger M. Systematic reviews in health care: diagnosis. BMJ 2009;338:b2706.
18. Tonelli M, Rochester D, Goldstein M. Incidence of hospitalization for heart failure and case-fatality among 3.25 million people with and without diabetes mellitus. Circulation 2018;138:2774–2786.
19. Roche MM, Wang PP. Sex differences in all-cause and cardiovascular mortality, hospitalization for individuals with and without diabetes, and patients with diabetes diagnosed early and late. Diabetes Care 2013;36:2582–2590.
20. Bragg F, Holmes MV, Iona A, Guo Y, Du H, Chen Y, Bian Z, Yang L, Herttington W, Bennett D, Turnbull I, Liu Y, Feng S, Chen J, Clarke R, Collins R, Peto R, Udd L, Chen Z. Association between diabetes and cause-specific mortality in rural and urban areas of China. JAMA 2017;317:280–289.
21. Haist T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, Torp-Pedersen C. Mortality and cardiovascular disease in type 1 and type 2 diabetes. Exp Diabetes Res 2012;2012:570598.
22. Hyun KK, Redfern J, Patel A, Peiris D, Brieger D, Sullivan D, Harris M, Sattar N, Fischbacher C, Kristensen SL, McMurray J, Colhoun HM, Wild SH. Incidence of hospitalization for heart failure and case-fatality among 3.25 million people with and without diabetes mellitus. Circulation 2018;138:2774–2786.
23. Schramm TK, Gislason GH, Køber L, Rasmussen S, Rasmussen JN, Abildstrøm M, Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. BMJ Open 2016;6:e012832.
24. Liang H, Vallarino C, Joseph G, Manne S, Perez A, Zhang S. Increased risk of subclinical inflammation in type 2 diabetes. Exp Diabetes Res 2012;2012:570598.
25. Liang H, Vallarino C, Joseph G, Manne S, Perez A, Zhang S. Increased risk of subclinical inflammation in type 2 diabetes patients. Exp Diabetes Res 2012;2012:570598.
26. Liang H, Vallarino C, Joseph G, Manne S, Perez A, Zhang S. Increased risk of subclinical inflammation in type 2 diabetes patients. Exp Diabetes Res 2012;2012:570598.
27. Hout D, Wang H, Wang Y, Wang Y, Wang Y, Wang Y, Wang Y, Wang Y. Recurrent stroke in minor ischemic stroke or transient ischemic attack with metabolic syndrome and/or diabetes mellitus. J Am Heart Assoc 2018;7:658–660.
28. Hout D, Wang H, Wang Y, Wang Y, Wang Y, Wang Y, Wang Y, Wang Y. Recurrent stroke in minor ischemic stroke or transient ischemic attack with metabolic syndrome and/or diabetes mellitus. J Am Heart Assoc 2018;7:658–660.
29. Hout D, Wang H, Wang Y, Wang Y, Wang Y, Wang Y, Wang Y, Wang Y. Recurrent stroke in minor ischemic stroke or transient ischemic attack with metabolic syndrome and/or diabetes mellitus. J Am Heart Assoc 2018;7:658–660.
30. Ku¨mler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, Torp-Pedersen C. Mortality and cardiovascular disease in type 1 and type 2 diabetes. Exp Diabetes Res 2012;2012:570598.
31. Ku¨mler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, Torp-Pedersen C. Mortality and cardiovascular disease in type 1 and type 2 diabetes. Exp Diabetes Res 2012;2012:570598.
32. Ku¨mler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, Torp-Pedersen C. Mortality and cardiovascular disease in type 1 and type 2 diabetes. Exp Diabetes Res 2012;2012:570598.
33. Ku¨mler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, Torp-Pedersen C. Mortality and cardiovascular disease in type 1 and type 2 diabetes. Exp Diabetes Res 2012;2012:570598.
34. Ku¨mler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, Torp-Pedersen C. Mortality and cardiovascular disease in type 1 and type 2 diabetes. Exp Diabetes Res 2012;2012:570598.
35. Ku¨mler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, Torp-Pedersen C. Mortality and cardiovascular disease in type 1 and type 2 diabetes. Exp Diabetes Res 2012;2012:570598.
36. Ku¨mler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, Torp-Pedersen C. Mortality and cardiovascular disease in type 1 and type 2 diabetes. Exp Diabetes Res 2012;2012:570598.