Current Cardiology Reports (2019) 21: 21
https://doi.org/10.1007/s11886-019-1107-y

DIABETES AND CARDIOVASCULAR DISEASE (N WONG, SECTION EDITOR)

Epidemiology of Diabetes Mellitus and Cardiovascular Disease

Diana Glovaci[1] · Wenjun Fan[1] · Nathan D. Wong[1]

Published online: 4 March 2019

Abstract

Purpose of Review Diabetes mellitus (DM) has become a rising epidemic in the last century, more pressing in the last few decades with the exponential rise of obesity, and has become one of the leading causes of death worldwide.

Recent Findings Genetic variants have also been a new field of epidemiology research to determine the underlying genetic component of those risk factors and the association of DM with CVD.

Summary In light of its significant prevalence, patients remain unaware of their disease progression that arises from genetic and metabolic risk factors. As compared to non-diabetics, those with type 2 DM carry a higher mortality risk from cardiovascular disease (CVD) across different ethnicity groups and sex. The most common cardiovascular manifestations in those with DM include heart failure, peripheral arterial disease, and coronary heart disease. Although DM does predispose patients to CVD, it in fact is not a risk equivalent, but carries significant heterogeneity in risk for CVD.

Keywords Cardiovascular disease · Diabetes mellitus · Epidemiology

Introduction

Diabetes mellitus has become one the most pressing and prevalent issue in the last few decades, hand-in-hand with the rising obesity crisis, and is now the seventh leading cause of death in the USA as well as worldwide, with 5.2 million deaths globally attributed to diabetes, a mortality rate of 82.4 per 100,000 [1], with 252,806 deaths in the USA alone in 2015 [2]. In addition, DM poses as a major risk factor for the development of cardiovascular disease (CVD), which ultimately results as the most common cause of death in those with DM [3]. In addition to microvascular complications of DM, including nephropathy, retinopathy, and neuropathy; macrovascular complications also become more prevalent in the form of coronary artery disease, peripheral vascular disease, and carotid artery disease with the increasing duration of diabetes [4].

Prevalence of Diabetes Mellitus

DM is caused by issues with insulin production by the pancreas or resistance by end-organ tissues and presents as a high blood glucose or elevated glycosylated hemoglobin A1C. There are three types of DM in the form of type 1, type 2, and gestational diabetes. Type 1 DM usually presents in early childhood and adolescents, and accounts for 5–10% of DM diagnosis in the USA, as the most common chronic autoimmune disorders [5, 6]. Gestational DM occurs during the second or third trimester of pregnancy which complicates one in six live births, increases the future risk of those patients to type 2 DM with the incidence of 35–60% in the two decades after delivery or a 7.4-fold increased risk [7–12] (Fig. 1). In addition, gestational DM also puts the patient's offspring at risk for DM and obesity development both genetically and environmentally with the intrauterine diabetic environment. Type 2 DM, the most common form accounts for 90–95% of diagnosed DM and continues to be rapidly growing worldwide and in the USA [6, 13]. A total of 1.7 million new cases of

This article is part of the Topical Collection on *Diabetes and Cardiovascular Disease*

✉ Diana Glovaci
dglovaci@uci.edu

Wenjun Fan
wenjuf1@uci.edu

Nathan D. Wong
ndwong@uci.edu

[1] Department of Medicine, Heart Disease Prevention Program, Division of Cardiology, University of California, C240 Medical Sciences, Irvine, CA 92697, USA

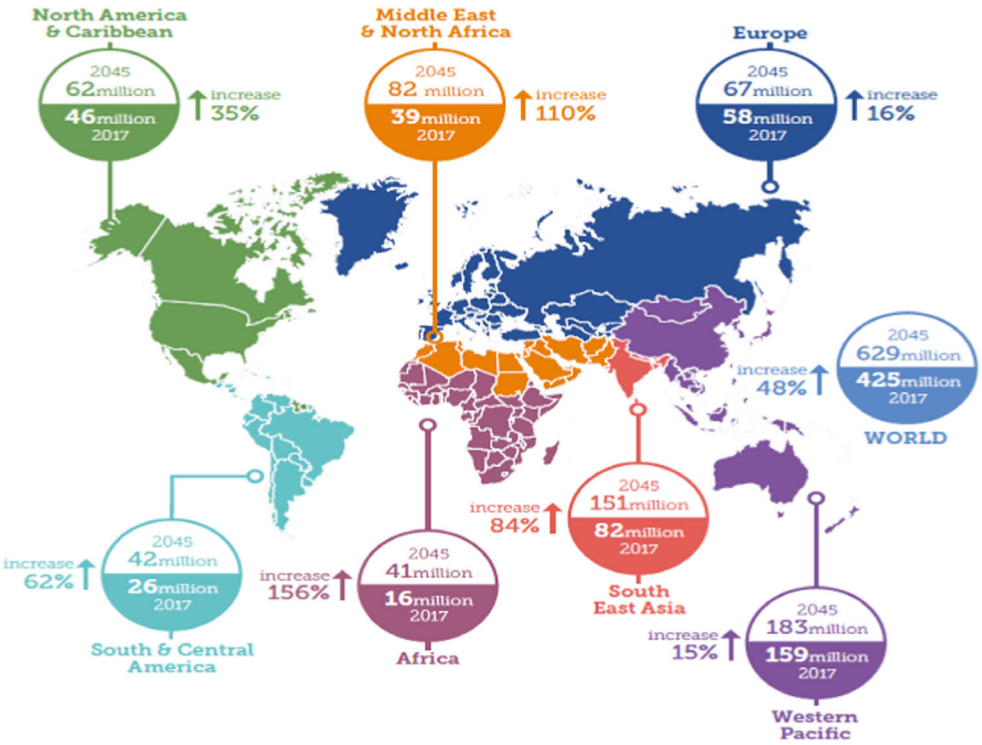

Fig. 1 Number of people with diabetes worldwide and per region in 2017 and 2045. (with permission from International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation, 2017. http://www.diabetesatlas.org) [12]

DM (types 1 and 2) were diagnosed in US adults over 20 years old in 2012 [13]. The exponential growth can be attributed to the increased proportion of an aging population, socioeconomic development, urbanization, highly processed diets, and decreased physical activity, to name a few. Due to the few symptoms or signs in the early years of type 2 DM, about half of people with DM do not know they have the disease, and symptoms go unnoticed and result in diabetic complications well before the diagnosis is made [12] (Fig. 1). These complications can result in cardiovascular disease in the forms of angina pectoris, myocardial infarction, stroke, peripheral artery disease, and congestive heart failure.

As described by the World Health Organization, DM of all types has exponentially grown in the past decades across the globe. The prevalence of DM increased from 108 million (4.7%) in 1980 to 425 million (8.5%) in 2017, and it is estimated to be 629 million by 2045 [12, 14] (Fig. 1). Paralleling the worldwide epidemic, according to NHANES 2011 to 2014, in the USA alone, there are about 23.4 million adults with diagnosed DM and an additional 7.6 million who are undiagnosed [3]. Despite this alarming prevalence of DM, there is still a lack of diagnosis affecting about 193 million people globally with the largest proportion, over 120 million in Southeast Asian and Western Pacific are unaware of their disease due to factors such as access to healthcare and silent development with minimal symptoms and signs [12] (Fig. 1). With China, India, and the USA topping the charts with 110, 69, and 23 million persons with DM in 2015, respectively, there were 16 million with DM in Africa, 58 million in Europe, 39 million (10.8%) in the Middle East and North Africa, 46 million (11%) in North America and Caribbean, 26 million (9.6%) in South and Central America, 82 million (19.3% of the total in the world) Southeast Asia, and 159 million (37.4% of total in the world) in the Western Pacific [12] (Fig. 1).

Risk Factors for Diabetes Mellitus and Cardiovascular Disease

Type 2 DM risk factors include a combination of both genetic and metabolic factors contributing to its prevalence. Non-modifiable factors include ethnicity, family history, previous gestational diabetes, and older age; in addition to modifiable factors including obesity, unhealthy diet, physical activity level, and smoking, all can contribute to the development of type 2 DM.

The pathophysiology of obesity is attributed to the end-organ tissue adipose cells being insulin-resistant to the increased influx of glucose [15, 16]. In addition, excessive adipose accumulation can increase circulating blood volume, in turn increase systemic resistance and cardiac output, causing right and left ventricular hypertrophy and ultimately right and left heart failure. Furthermore, obesity causes an increase in leptin and inflammatory markers such as CRP, which can further lead to worsening vascular and myocardial injury [17]. Compared to adults of normal weight, those with BMI of greater than 40 have increased odds of 7.37 (95% CI 6.39–8.5) for diagnosed diabetes, in addition to 6.39 OR (95% CI

5.67–7.16) for hypertension, and 1.88 (95% CI 1.67–2.13) for hypercholesterolemia [18]. Some prospective studies from Asia also show type 2 DM to be common in lower BMI groups; thus, Asians with lower BMI compared to European descent counterparts have higher prevalence of type 2 DM [19–22]. For example, although India has the lowest rate of obesity in the world [23], the prevalence of type 2 DM increased 10-fold over the past 40 years, with 67 million in 2014 which projected to double by 2030 [24, 25]. Thoughts on why this is the case revolve around the centrally located obesity around the abdomen, genetics, and dietary causes.

The modern sedentary lifestyle is another crucial modifiable risk factor for type 2 DM and CVD; in the Women's Health Study, a 6.9-year follow-up of 38,000 US female health professionals from age 45 and older, participants with reported walking 2–3 h a week were 34% less likely to develop DM than those not walking, and those who walked 1 h a week was associated with 50% reduction in CHD risk over those 7 years [26, 27]. In the Kuipio Ischemic Heart Disease Risk Factor Study, which followed 897 Finnish men from 42 to 60 years old for 4.2 years, those who performed at least 40 min a week of physical activity with 5.5 metabolic equivalents were 56% less likely to develop DM than those who did not, after adjusting for effects of BMI and other covariates [28]. In the 8-year follow-up of 2449 with DM in the National Health Interview Survey, walking 2 h/week was associated with 41% reduction in CVD mortality compared to non-walkers [29].

Dyslipidemia and hypertension also compound risk for further development of CVD [30, 31] due to their effects on endothelial dysfunction that can further accelerate atherosclerosis [8]. The prevalence of concurrent DM, hypertension, and hypercholesterolemia in US adults has also increased from 3% in 1999–2000 to 6.3% in 2011–2012 [32]. One study among 371,221 veterans demonstrated two thirds of diabetic patients co-exist with dyslipidemia and hypertension, at a rate of double than non-diabetic vets [33]. A prospective cohort study of 12,550 adults that type 2 DM development occurred 2.5 times more in those with hypertension [34]. In the United Kingdom Prospective Diabetes Study, with more intensive blood pressure reduction, there was a far more powerful benefit to CVD risk reduction, as well as diabetic microvascular and macrovascular complications in those with a mean BP of 144/82 mmHg compared to those with a mean of 154/87 mmHg [35–37].

Other major cardiovascular risk factors including cigarette smoking, hypertension, and high serum cholesterol also act as independent contributors to CVD in patients with DM, across multiple racial and ethnic groups, as well in such prospective studies as Framingham, Honolulu, and San Antonio Heart Studies [38].

Furthermore, inflammatory markers such as C-reactive protein (CRP) in diabetic patients can also signify further risk of CVD and peripheral artery disease (PAD). CVD and PAD have been shown to be more common in those with metabolic syndrome or DM who have elevated CRP, thus enhancing more prognostic information in DM patients, in addition to other traditional risk factors [39, 40]. In a large multiethnic cohort study, the addition of coronary artery calcium score to global risk assessment was also associated with significantly improved long-term risk re-classification in those with metabolic syndrome and diabetes [41].

Morbidity and Mortality of Cardiovascular Disease in Diabetes Mellitus

Cardiovascular deaths account for 44% of death in those with type 1 DM and 52% of deaths in type 2 DM [42]. Type 2 DM carries a two to six times risk of death from cardiovascular etiologies, such that age-adjusted prevalence of white Americans for coronary heart disease is double in those with type 2 DM than those without [43–46]. Initial presentations of CVD in DM most commonly manifest as peripheral arterial disease (16.2% or three times greater) and heart failure (14.7%) followed by angina and non-fatal MI. This suggests the need for earlier screening of subclinical PAD and HF [47] (Fig. 2). In the San Antonio Heart Study, 4875 patients followed over 7–8 years demonstrated that DM was significantly associated with increased all-cause mortality (RR 2.1, 95% CI 1.3–3.5 in men; RR 8.5 95% CI, 2.8–25.2 in women) [48]. Heart failure risk rose to 40% in DM patients compared to non-diabetics with age-adjusted odd ratio of 2.8 (95% CI, 2.2–3.6), and had a two to three times greater risk of development [49]. In the National Health and Nutrition Examination Survey cohort (NHANES), 26.3% of strokes were associated with diabetes, with a 2-fold greater risk in those with diabetes for ischemic strokes and 50% increase for hemorrhagic strokes [50, 51]. Mortality rates post-MI are also higher in diabetics than non-diabetic patients, and the cardiovascular death rate is 4.4-fold increased in diabetes alone without other traditional cardiovascular risk factors in comparison to non-diabetics in the same age groups [52–55].

Ethnic differences in CVD and DM prevalence have also been evident. From the Heart Disease and Stroke Statistics 2018 update, the prevalence of heart disease across differing ethnic groups were 11.1% in non-Hispanic White, 10.3% Black or African Americans, 7.8% Hispanic or Latinos, 6.0% Asians, 13.7% American Indians or Alaska Natives, and 19.1% native Hawaiians or other Pacific Islanders [3]. In comparison, the prevalence of DM is significantly higher in South Asians (from India, Pakistan, Sri Lanka, Bangladesh, Nepal, Bhutan, Maldives) compared to other US ethnic populations, with India alone accounting for 1/5 CHD deaths

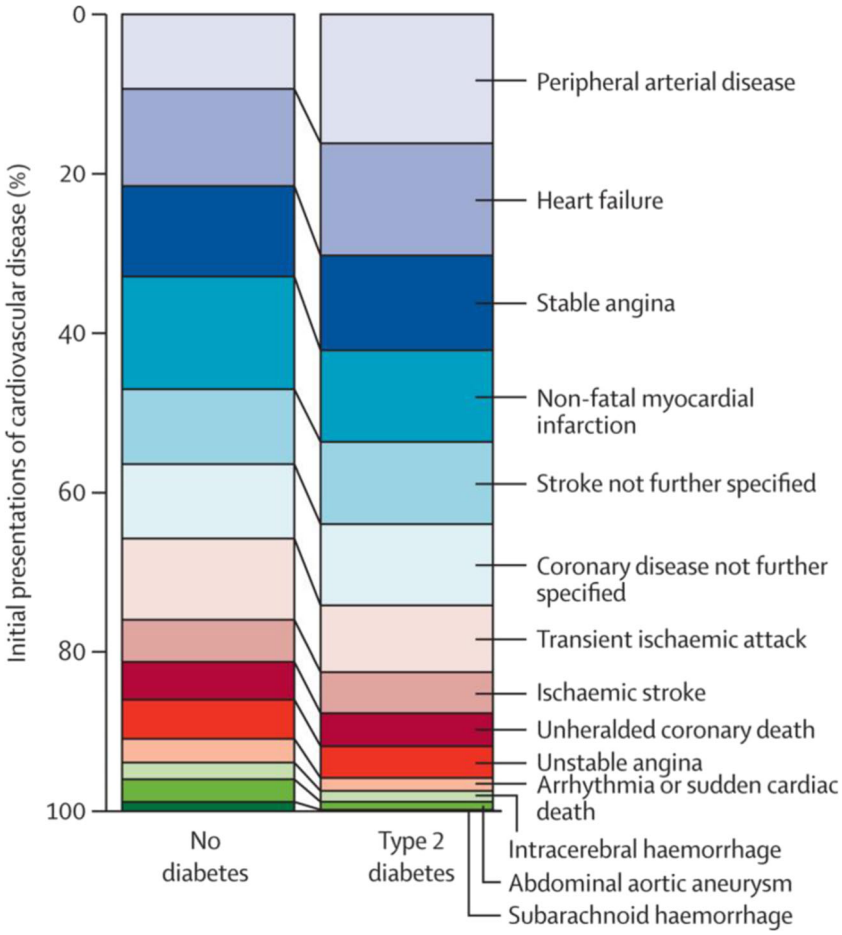

Fig. 2 Distribution of initial presentations of cardiovascular disease in participants with and without type 2 diabetes and no history of cardiovascular disease. (with permission from Shah et al. Lancet Diabetes Endocrinol. 2015;3:105–13) [47]

worldwide [56]. In a recent population-based study of South Asians in the USA, type 2 DM prevalence was 17.4%, compared to non-Hispanic White (7.8%), non-Hispanic Black (13%), and Hispanic Latinos (10.2%) [57]. South Asian populations also had the largest proportion of cardiovascular deaths of 1.7 million in 2013, with an increase of 97.4% since 1990 [58].

Gender Differences in DM and CVD Risk

Several studies have also shown different CVD risks across gender among those with DM. The Early Rancho Bernando Study demonstrated that men with DM had a 2.4-fold increased risk of ischemic heart disease compared to men without, while diabetic women had a 3.5 increased risk [59, 60]. Additionally, there was a 3-fold excess fatal CHD risk in type 2 DM females, with a hazard ratio of 14.74 (95% CI 6.16–35.27) compared to men (HR 3.77; 95% CI, 2.52–5.65) [61]. Not only was there a higher mortality for MI in diabetic women compared to men, myocardial infarction also occurred earlier in women [62, 63]. For stroke analysis, a comprehensive systematic review and meta-analysis from 64 cohorts with 12,000 strokes, the adjusted RR for stroke and DM was 2.28 (95% CI, 1.93–2.69) for women vs. 1.83 (95% CI, 1.60–2.08) in men [64]. In addition, in the Framingham Study with 36 years of follow-up data, diabetic women were also noted to have greater age-adjusted risks of PAD (risk ratio 6.4 vs. 2.9 in men), heart failure (7.8 vs. 4.4), as well as overall CVD events (3.7 vs. 2.2) when compared to diabetic men [65].

Diabetes as a CVD Risk Equivalent

There still remains debate if diabetes can be considered as a CVD risk equivalent with such a strong association and relation with diabetes and CVD development [66, 67]. It has previously been shown that a diabetic patient without a previous MI compared to a non-diabetic patient with a prior MI have similar risk for CHD death in both men and women [68]. As compared to women without DM and CHD at baseline, age-adjusted RR of overall mortality was 3.39 (95% CI, 3.08–3.73) in those with diabetes and no CHD, 3.00 (95% CI, 2.50–3.60) for a history of CHD and no DM [69]. However, debate still remains since there has also been an opposing view. One meta-analysis of 13 studies with a total of 45,108

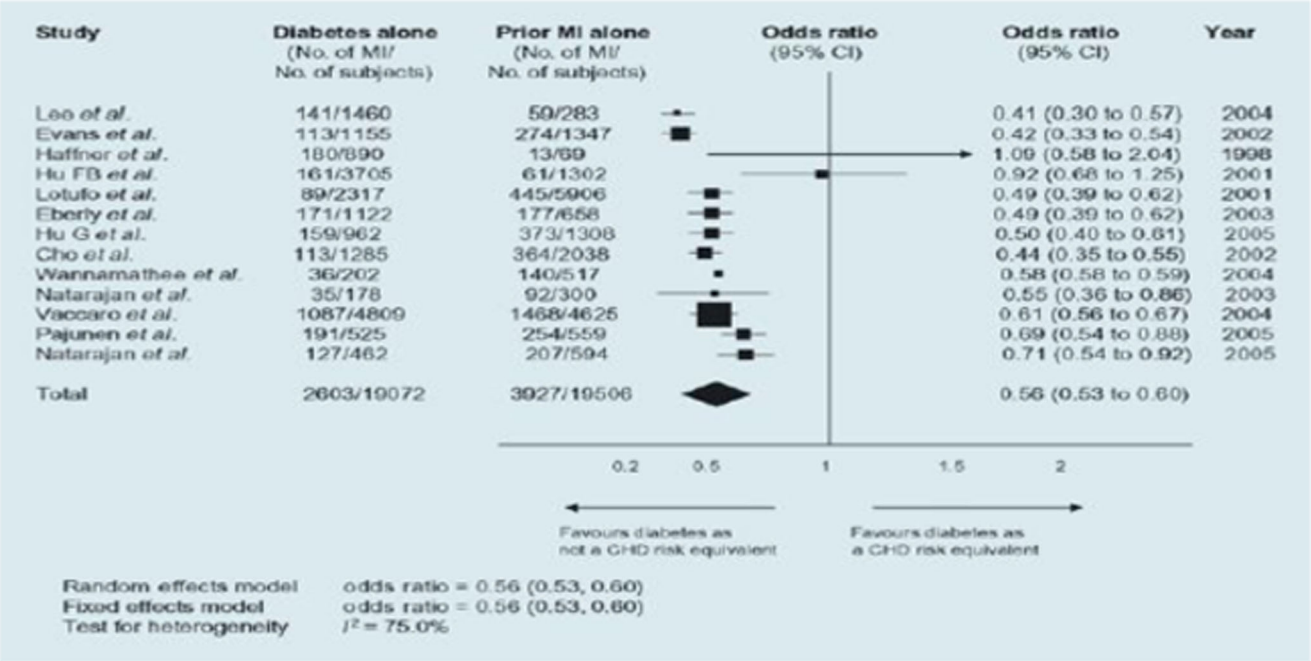

Fig. 3 Meta-analysis demonstrating diabetes is not a CHD equivalent. (with permission from Bulugahapitiya et al. Diabet Med 2009; 26:142–148) [70]

patients demonstrated that those with DM have actually a lower CHD event rate compared to known CHD, while another study showed that global CVD risk in US adults demonstrated that half of women and one third of men with DM are at low or intermediate CVD risk [70, 71] (Fig. 3). NHANES studies also show that the average Framingham and UKPDS 10-year risk for CHD are 12.6% in diabetic women and 11.6% in men, and demonstrate that diabetes does not reach the CHD risk equivalence cutpoint of 20% 10-year risk [72]. In the Kaiser Permanente Northern California study, DM alone was not a CHD risk equivalent since DM alone had a HR 1.7 (1.66–1.74), a CHD alone 2.8 (2.7–2.85), and a combined 3.9 (3.8–4.0) [73]. Based on the level of coronary calcium, the Multiethnic Study of Atherosclerosis showed there was in fact a 10-fold variation in CHD risk in those with DM, ranging from 0.4 to 4% per year for annual CHD event rates, further demonstrating that DM is not a risk equivalent, and that perhaps the extent of subclinical atherosclerosis itself rather than DM status is a stronger driver of risk [74].

Genetic Variants

Mendelian randomization analyses also support a causal role for DM through its association of high glucose levels on CAD. Using the information from 59 other genetic variants in one study, DM was associated to CAD with an odds ratio of 1.63 (95% CI, 1.23–2.07; $P < 0.002$). Of those variants, nine were with an odds ratio of 1.53 for every 1% increase in HbA1C (95%CI, 1.14–2.05; $P < 0.023$) to the increased risk of CAD, while this effect was non-significant among 30 genetic variants associated with fasting glucose per mmol/L (OR, 1.18; 95% CI, 0.97–1.42; P ¼ 0.102) [75], thus suggesting a causal relationship between type 2 diabetes and CAD at a genetic level [76]. Debate still remains if the association between DM and CVD is related to diabetes status itself or the risk factors diabetic patients are prone to. Meanwhile, other studies focus on the relationship among risk factors to diabetes, with one such link between lipid variants and diabetes status [77]. However, in other studies, genetic variants for elevated fasting plasma glucose but not genetically elevated risk of type 2 diabetes were associated with arterial stiffness, thus suggesting a causal associated between hyperglycemia and atherosclerosis, independently of type 2 diabetes [78••]. Several Mendelian randomization analyses have shown that diabetes is associated with CAD, independent of other risk factors (odds ratio [OR], 1.63; 95% confidence interval [CI], 1.23–2.07; $P = 0.002$) [79••].

Conclusion

With the rapid and alarming growth of DM, the concern lies in both the vast prevalence as well as the major complications associated with DM, especially CVD. More attention needs to be paid to its prevention and targeting genetic variants for risk factors of diabetes and the genetic predisposition of diabetes itself.

Compliance with Ethical Standards

Conflict of Interest Diana Glovaci and Wenjun Fan declare that they have no conflict of interest.

Nathan D. Wong reports grants from Amgen, Amarin, Boehringer-Ingelheim, and Novo Nordisk, and personal fees from Astra Zeneca.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Global Burden of Disease Study 2015. Global burden of disease study 2015 (GBD 2015) results. Seattle: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2016. http://ghdx.healthdata.org/gbd-results-tool. Accessed 9 Aug 2018.
2. National Center for Health Statistics. Mortality multiple cause micro-data files, 2015: public-use data file and documentation: NHLBI tabulations. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm. Accessed 23 Dec 2018.
3. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation. 2018;137(12):e67–e492.
4. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA. 2002;287:2570–81.
5. Redberg RF, Greenland P, Fuster V, Pyörälä K, Blair SN, Folsom AR, et al. Prevention Conference VI: Diabetes and cardiovascular disease: writing group III: risk assessment in persons with diabetes. Circulation. 2002;105(18):e144–52.
6. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. N Engl J Med. 2017;376:1419–29.
7. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta: US Department of health and human services, Centers for Disease Control and Prevention; 2011.
8. Dokken B. The pathophysiology of cardiovascular disease and diabetes: beyond blood pressure and lipids. Diabetes Spectr. 2008;21(3):160–5.
9. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009;373:1773–9.
10. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care. 2002;25:1862–8.
11. Lee AJ, Hiscock RJ, Wein P, Walker SP, Permezel M. Gestational diabetes mellitus: clinical predictors and long-term risk of developing type 2 diabetes: a retrospective cohort study using survival analysis. Diabetes Care. 2007;30:878–83.
12. International Diabetes Federation. IDF diabetes atlas. 8th ed. Brussels: International Diabetes Federation; 2017. http://www.diabetesatlas.org. Accessed 9 Aug 2018.
13. Centers for Disease Control and Prevention. National diabetes statistics report: estimates of diabetes and its burden in the United States, 2014. Atlanta: US Department of Health and Human Services; 2014.
14. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;387:1513–30. https://doi.org/10.1016/S0140-6736(16)00618-8.
15. Hardy OT, Czech MP, Corvera S. What causes the insulin resistance underlying obesity? Curr Opin Endocrinol Diabetes Obes. 2012;19:81.
16. [No authors listed]. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. National Institutes of Health. Obes Res. 1998;6(Suppl 2):51S–209S.
17. Lavie C, Milani R, Ventura H. Obesity and cardiovascular disease risk factor, paradox and impact of weight loss. JACC. 2009;53(21):1925–32.
18. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA. 2003;289:76–9.
19. Ko GT, Chan JC, Woo J, Lau E, Yeung VT, Chow CC, et al. Simple anthropometric indexes and cardiovascular risk factors in Chinese. Int J Obes Relat Metab Disord. 1997;21:995–1001.
20. Oh SW, Shin SA, Yun YH, Yoo T, Huh BY. Cut-off point of BMI and obesity related comorbidities and mortality in middle-aged Koreans. Obes Res. 2004;12:2031–40.
21. Shin CS, Lee HK, Koh CS, Kim YI, Shin YS, Yoo KY, et al. Risk factors for the development of NIDDM in Yonchon County, Korea. Diabetes Care. 1997;20:1842–6.
22. Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, et al. Epidemic obesity and type 2 diabetes in Asia. Lancet. 2006;368:1681–8.
23. OECD. Obesity update. OECD Health Statistics 2014. 2014. Available at: http://www.oecd.org/els/health-systems/Obesity-Update-2014.pdf. Accessed 9 Aug 2018.
24. Scully T. Diabetes in numbers. Nature. 2012;485:S2–3.
25. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Austr Med J. 2014;7:45–8.
26. Weinstein AR, Sesso HD, Lee IM, Cook NR, Manson JE, Buring JE, et al. Relationship of physical activity vs body mass index with type 2 diabetes in women. JAMA. 2004;292:1188–94.
27. Lee IM, Rexrode KM, Cook NR, Manson JE, Buring JE. Physical activity and coronary heart disease in women: is 'no pain, no gain' passe? JAMA. 2001;285:1447–54.
28. Lynch J, Helmrich SP, Lakka TA, Kaplan GA, Cohen RD, Salonen R, et al. Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle aged men. Arch Intern Med. 1996;156:1307–14.
29. Gregg EW, Gerzoff RB, Caspersen CJ, Williamson DF, Narayan KV. Relationship of walking to mortality among US adults with diabetes. Arch Intern Med. 2003;163:1440–7.
30. Shurtleff D. The Framingham study: an epidemiologic investigation of cardiovascular disease, section 26. Washington, DC: US Government Printing Office; 1970.
31. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 1991;265:3255–64.
32. Song Y, Liu X, Zhu X, Zhao B, Hu B, Sheng X, et al. Increasing trend of diabetes combined with hypertension or

hypercholesterolemia: NHANES data analysis 1999-2012. Sci Rep. 2016;6:36093. https://doi.org/10.1038/srep36093.
33. Johnson ML, Pietz K, Battleman DS, Beyth RJ. Prevalence of comorbid hypertension and dyslipidemia and associated cardiovascular disease. Am J Manag Care. 2004;10:926–32.
34. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. N Engl J Med. 2000;342:905–12.
35. UKPDS Group. UK prospective diabetes study 38: tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. BMJ. 1998;317:703–13.
36. UKPDS Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ. 1998;317:713–20.
37. American Diabetes Association. Implications of the United Kingdom prospective diabetes study. Diabetes Care. 2000;23(Suppl 1):S28–32.
38. Fan W. Epidemiology in diabetes mellitus and cardiovascular disease. Cardiovasc Endocrinol. 2017;6(1):8–16.
39. Malik S, Wong ND, Franklin S, Pio J, Fairchild C, Chen R. Cardiovascular disease in U.S. patients with metabolic syndrome, diabetes, and elevated C-reactive protein. Diabetes Care. 2005 Jul;28(7):1833–4.
40. Vu JD, Vu JB, Pio JR, Malik S, Franklin SS, Chen RS, et al. Impact of C-reactive protein on the likelihood of peripheral arterial disease in United States adults with the metabolic syndrome, diabetes mellitus, and preexisting cardiovascular disease. Am J Cardiol. 2005;96(5):655–8.
41. Malik S, Zhao Y, Budoff M, Nasir K, Blumenthal R, Bertoni A, et al. Coronary artery calcium score for long-term risk classification in individuals with type 2 diabetes and metabolic syndrome from the multi-ethnic study of atherosclerosis. JAMA Cardiol. 2017;2(12):1332–40.
42. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. WHO multinational study group. Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. Diabetologia. 2001;44(Suppl 2):S14–21.
43. Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. JAMA. 1999;281:1291–7.
44. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. Jama. 1979;241:2035–8.
45. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Arch Intern Med. 1991;151:1141–7.
46. Wingard DL, Barrett-Connor E. Heart disease and diabetes. In: Harris MI, Cowie CC, Stern MP, Boyko EJ, Rieber GE, Bennett PH, editors. Diabetes in America. 2nd ed. Bethesda: National Institutes of Health; 1995. p. 429–48.
47. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocrinol. 2015;3:105–13.
48. Wei M, Gaskill SP, Haffner SM, Stern MP. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality: the San Antonio heart study. Diabetes Care. 1998;21:1167–72.
49. Go AS, Mozaffarian D, Roger VL. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation. 2014;129:e28–e292.
50. Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH, Folsom AR. Risk factors for ischemic stroke subtypes the atherosclerosis risk in communities study. Stroke. 2006;37:2493–8.
51. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative metaanalysis of 102 prospective studies. Lancet. 2010;375:2215–22.
52. Barbash GI, White HD, Modan M, Van de Werf F. Significance of diabetes mellitus in patients with acute myocardial infarction receiving thrombolytic therapy. J Am Coll Cardiol. 1993;22:707–13.
53. Zuanetti G, Latini R, Maggioni AP, Santoro L, Franzosi MG. GISSI-2 investigators. Influence of diabetes on mortality in acute myocardial infarction: data from the GISSI-2 study. J Am Coll Cardiol. 1993;22:1788–94.
54. Granger CB, Califf RM, Young S, Candela R, Samara J, Worley S, et al. Outcome of patients with diabetes mellitus and acute myocardial infarction treated with thrombolytic agents. J Am Coll Cardiol. 1993;21:920–5.
55. Abbud ZA, Shindler DM, Wilson AC, Kostis JB. Myocardial infarction data acquisition system study group. Effect of diabetes mellitus on short-and long-term mortality rates of patients with acute myocardial infarction: a statewide study. Am Heart J. 1995;130:51–8.
56. Kanaya AM, Wassel CL, Mathur D, Stewart A, Herrington D, Budoff MJ, et al. Prevalence and correlates of diabetes in South Asian Indians in the 14 Cardiovascular Endocrinology 2017, Vol 6 No 1 United States: findings from the metabolic syndrome and atherosclerosis in South Asians living in America study and the multi-ethnic study of atherosclerosis. Metab Syndr Relat Disord. 2010;8:157–64.
57. Misra R, Patel T, Kotha P, Raji A, Ganda O, Banerji M, et al. Prevalence of diabetes, metabolic syndrome, and cardiovascular risk factors in US Asian Indians: results from a national study. J Diabetes Complicat. 2010;24:145–53.
58. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. N Engl J Med. 2015;372:1333–41.
59. Barrett-Connor E, Wingard DL. Sex differential in ischemic heart disease mortality in diabetics: a prospective population-based study. Am J Epidemiol. 1983;118:489–96.
60. Wenger NK. You've come a long way, baby cardiovascular health and disease in women: problems and prospects. Circulation. 2004;109:558–60.
61. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Arch Intern Med. 1991;151:1141–7.
62. Hu G, Jousilahti P, Qiao Q, Katoh S, Tuomilehto J. Sex differences in cardiovascular and total mortality among diabetic and non-diabetic individuals with or without history of myocardial infarction. Diabetologia. 2005;48:856–61.
63. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ. 2006;332:73–8.
64. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. Lancet. 2014;383:1973–80.
65. Fox CS. Cardiovascular disease risk factors, type 2 diabetes mellitus, and the Framingham heart study. Trends Cardiovasc Med. 2010;20(3):90–5. https://doi.org/10.1016/j.tcm.2010.08.001.
66. Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, et al. OASIS registry investigators. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction results of the OASIS (organization to assess strategies for ischemic syndromes) registry. Circulation. 2000;102:1014–9.
67. Mukamal KJ, Nesto RW, Cohen MC, Muller JE, Maclure M, Sherwood JB, et al. Impact of diabetes on long-term survival after acute myocardial infarction comparability of risk with prior myocardial infarction. Diabetes Care. 2001;24:1422–7.
68. Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Type 2 diabetes as a 'coronary heart disease equivalent': an 18-year

prospective population-based study in Finnish subjects. Diabetes Care. 2005;28:2901–7.

69. Hu FB, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. Arch Intern Med. 2001;161:1717–23.
70. Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med. 2009;26:142–8.
71. Wong ND, Glovaci D, Wong K, Malik S, Franklin SS, Wygant G, et al. Global cardiovascular disease risk assessment in United States adults with diabetes. Diab Vasc Dis Res. 2012;9:146–52.
72. Ford ES. Trends in the risk for coronary heart disease among adults with diagnosed diabetes in the US findings from the national health and nutrition examination survey, 1999–2008. Diabetes Care. 2011;34:1337–43.
73. Rana JS, Liu JY, Moffet HH, Jaffe M, Karter AJ. Diabetes and prior coronary heart disease are not necessarily risk equivalent for future coronary heart disease events. J Gen Intern Med. 2016;31:387–93.
74. Malik S, Budoff MJ, Katz R, Blumenthal RS, Bertoni AG, Nasir K, et al. Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and diabetes: the multi-ethnic study of atherosclerosis. Diabetes Care. 2011;34(10):2285–90. https://doi.org/10.2337/dc11-0816.
75. Ross S, Hertzel G, Eikelboom J, Anand S, Yusufl S, Pare G. Mendelian randomization analysis supports the causal role of dysglycaemia and diabetes in the risk of coronary artery disease. Eur Heart J. 2015;36:1454–62.
76. Ahmad OS, Morris JA, Mujammami M, Forgetta V, Leong A, Li R, et al. A Mendelian randomization study of the effect of type-2 diabetes on coronary heart disease. Nat Commun. 2015;6:7060. https://doi.org/10.1038/ncomms8060.
77. Fall T, Xie W, Poon W, Yaghootkar H, Magi R, et al. Using genetic variants to assess the relationship between circulating lipids and type 2 diabetes. Diabetes. 2015;64(7):2676–84. https://doi.org/10.2337/db14-1710.
78.•• Gottsäter M, Hindy G, Orho-Melander M, Nilsson PM, Melander O. A genetic risk score for fasting plasma glucose is independently associated with arterial stiffness: a Mendelian randomization study. J Hypertens. 2018;36(4):809–14. https://doi.org/10.1097/HJH.0000000000001646 **This study demonstrated that the component of genetically elevated fasting glucose, not necessarily genetically elevated risk of type 2 diabetes was associated with arterial stiffness.**
79.•• Ross S, Hertzel G, Pare G. The genetic link between diabetes and atherosclerosis. Can J Cardiol. 2018;34(5):565–74 **This article illustrates the potential of genetic studies to understand the relationships among atherosclerotic disease, elevated fasting glucose, and diabetes.**