Diabetes and COVID-19–Related Mortality in Women and Men in the UK Biobank: Comparisons With Influenza/Pneumonia and Coronary Heart Disease

Marit de Jong,[1] Mark Woodward,[2,3,4] and Sanne A.E. Peters[1,2,3]

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Individuals with diabetes are at increased risk of poor outcomes from coronavirus disease 2019 (COVID-19) (1–4). Whether the excess risk of COVID-19 mortality associated with impaired glucose tolerance and diabetes is different between women and men is uncertain. We used data from the UK Biobank to investigate the sex-specific associations, and sex differences, between diabetes status, HbA_{1c}, and risk of COVID-19 mortality. As comparison, we also examined sex-specific associations of death by influenza/pneumonia, a major cause of death from respiratory disease prior to COVID-19, and fatal coronary heart disease (CHD), a condition for which sex differences are well established.

The UK Biobank is a prospective cohort study including ~500,000 participants aged 40–69 years at baseline between 2006 and 2010 (5). Follow-up for cause-specific mortality was conducted to 30 June 2020 through linkage with the national death register. Cox regression was used to obtain sex-specific hazard ratios (HRs) and 95% CIs for mortality from COVID-19, influenza/pneumonia, and CHD by diabetes status and HbA_{1c} level. For analyses involving >2 groups, 95% CIs were estimated through floating absolute risks. Adjustments were made for age, BMI, socioeconomic status, smoking, systolic blood pressure, antihypertensive medication, total cholesterol, and lipid-lowering medication. Models for levels of HbA_{1c} (≤6.5% [48 mmol/mol], >6.5% to ≤7.5%, and >7.5% [58 mmol/mol]) were additionally adjusted for glucose-lowering medication, and models for 1% HbA_{1c} change (irrespective of diabetes) were additionally adjusted for glucose-lowering medication and diabetes. Interactions between each variable and sex were added to the model to obtain the women-to-men ratio of HRs for each risk factor.

Overall, 501,884 participants (54% women) were included. At baseline, 7.1% of men and 3.9% of women were previously diagnosed with diabetes, with median HbA_{1c} of 7.0% (53 mmol/mol) and 6.9% (52 mmol/mol), respectively. Over a mean follow-up of 11.2 years, 408 participants (36% women) died of COVID-19, 549 (36% women) died of influenza/pneumonia, and 3,347 (19% women) died of CHD. Diabetes was associated with greater excess risk of death from COVID-19, influenza/pneumonia, and CHD in men and women **(**Table 1**)**. In both sexes, the magnitude of the association was strongest for CHD with a HR of 3.17 in women and 1.93 in men, followed by influenza/pneumonia (2.06 and 1.80) and COVID-19 (1.52 and 1.73). For COVID-19 and influenza/pneumonia, the magnitude of the association with diabetes was similar between the sexes. For CHD, diabetes was associated with a 64% greater excess risk in women compared with men. Higher levels of HbA_{1c} were not associated with greater risk of COVID-19 or influenza/pneumonia death in women. In men, an HbA_{1c} >7.5% (58 mmol/mol), compared with no diabetes, was associated with a greater risk of COVID-19 or influenza/pneumonia death. Each 1% higher HbA_{1c} was associated with a 9% greater risk of influenza/pneumonia death in men. By comparison, higher levels of HbA_{1c} were associated with greater risk of fatal CHD in both sexes, and the magnitude of the association between 1% higher HbA_{1c} and CHD was 9% stronger in women compared with men.

This study shows that diabetes is associated with a greater risk of fatal COVID-19, influenza/pneumonia, and CHD in both sexes. However, unlike for CHD, there are no sex differences in the association between diabetes and death from COVID-19 or influenza/pneumonia. Our finding that diabetes is associated with higher risk of COVID-19 mortality is consistent with other studies (1–4). A study of 61 million individuals in England showed that over a third of all in-hospital COVID-19–related

[1]*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands*
[2]*The George Institute for Global Health, Imperial College London, London, U.K.*
[3]*The George Institute for Global Health, University of New South Wales, Sydney, Australia*
[4]*Department of Epidemiology, Johns Hopkins University, Baltimore, MD*

Corresponding author: Sanne A.E. Peters, speters@georgeinstitute.org.uk

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Table 1—Adjusted HRs (95% CIs) and women-to-men ratio of HRs for death from COVID-19, influenza/pneumonia, or CHD associated with diabetes status and HbA_{1c} levels and per 1% change in HbA_{1c}

	Death from COVID-19			Death from influenza/pneumonia			Death from CHD		
	Women	Men	RHR	Women	Men	RHR	Women	Men	RHR
Previously diagnosed diabetes									
vs. not	1.52 (0.82; 2.82)	1.73 (1.19; 2.52)	0.88 (0.43; 1.81)	2.06 (1.30; 3.28)	1.80 (1.32; 2.44)	1.15 (0.66; 2.00)	3.17 (2.51; 3.99)	1.93 (1.73; 2.15)	1.64 (1.27; 2.12)
Diabetes status									
No diabetes	1.00 (0.77; 1.30)	1.00 (0.82; 1.22)	1.00 (0.72; 1.39)	1.00 (0.79; 1.26)	1.00 (0.84; 1.19)	1.00 (0.75; 1.34)	1.00 (0.87; 1.15)	1.00 (0.94; 1.07)	1.00 (0.86; 1.16)
Prediabetes	0.93 (0.64; 1.35)	0.94 (0.67; 1.31)	0.99 (0.60; 1.63)	1.15 (0.85; 1.57)	1.11 (0.85; 1.45)	1.04 (0.69; 1.57)	1.55 (1.32; 1.82)	1.26 (1.15; 1.37)	1.23 (1.03; 1.48)
Undiagnosed diabetes	1.27 (0.32; 5.08)	3.51 (1.82; 6.78)	0.36 (0.08; 1.68)	0.73 (0.10; 5.15)	1.71 (0.71; 4.12)	0.42 (0.05; 3.64)	1.68 (0.80; 3.53)	2.17 (1.69; 2.80)	0.77 (0.35; 1.70)
Previously diagnosed diabetes	1.51 (0.85; 2.69)	1.80 (1.29; 2.52)	0.84 (0.43; 1.64)	2.17 (1.42; 3.31)	1.89 (1.44; 2.47)	1.15 (0.69; 1.89)	3.76 (3.07; 4.61)	2.12 (1.93; 2.33)	1.78 (1.42; 2.22)
HbA_{1c} levels									
No previously diagnosed diabetes	1.00 (0.45; 2.21)	1.00 (0.62; 1.61)	1.00 (0.39; 2.53)	1.00 (0.49; 2.05)	1.00 (0.66; 1.51)	1.00 (0.44; 2.30)	1.00 (0.75; 1.33)	1.00 (0.87; 1.15)	1.00 (0.73; 1.38)
≤6.5%	0.82 (0.28; 2.39)	1.38 (0.85; 2.23)	0.60 (0.18; 1.92)	1.01 (0.52; 1.96)	1.27 (0.86; 1.87)	0.80 (0.37; 1.71)	2.18 (1.62; 2.94)	1.48 (1.29; 1.69)	1.48 (1.06; 2.05)
>6.5% to ≤7.5%	1.10 (0.35; 3.45)	1.69 (0.93; 3.07)	0.65 (0.18; 2.36)	1.42 (0.77; 2.62)	1.26 (0.78; 2.03)	1.13 (0.52; 2.46)	2.18 (1.53; 3.10)	1.62 (1.38; 1.89)	1.35 (0.92; 1.99)
>7.5%	2.67 (0.98; 7.22)	2.25 (1.20; 4.24)	1.18 (0.36; 3.85)	0.94 (0.43; 2.07)	1.69 (1.04; 2.74)	0.56 (0.22; 1.40)	3.70 (2.65; 5.15)	2.08 (1.77; 2.45)	1.77 (1.22; 2.57)
Per 1% HbA_{1c} change	1.04 (0.76; 1.42)	1.10 (0.98; 1.22)	0.95 (0.68; 1.32)	1.06 (0.83; 1.35)	1.09 (1.00; 1.19)	0.97 (0.75; 1.25)	1.21 (1.14; 1.29)	1.12 (1.09; 1.14)	1.09 (1.02; 1.16)

Analyses by diabetes and diabetes status were adjusted for age, BMI, socioeconomic status, smoking, systolic blood pressure, use of antihypertensive medication, total cholesterol, and use of lipid-lowering medication. Models for levels of HbA_{1c} were additionally adjusted for the use of glucose-lowering medication. Similar levels of adjustments were used for the analyses of 1% HbA_{1c} change, additionally adjusted for history of diabetes. For all analyses involving more than two groups, 95% CIs were estimated through floating absolute risks. RHR, women-to-men ratio of HRs. COVID-19 mortality was defined by ICD-10 code U072. Death from influenza/pneumonia was defined by ICD-10 codes J09, J13, J14, J100, J101, J108, J110, J111, J118, J121–J123, J128, J129, J150–J152, J154, J155, J159, J180, J181, and J189. Fatal CHD was defined by ICD-10 codes I200, I209, I213, I214, I219, I232, I248–I255, I258, and I259. HbA_{1c} 6.5% = 48 mmol/mol; HbA_{1c} 7.5% = 58 mmol/mol.

deaths occurred in those with diabetes, and those with diabetes had higher odds of in-hospital COVID-19–related death than those without diabetes (1). In contrast to our study, however, that study suggested that women with diabetes were at higher risk of COVID-19–related mortality than men (1). Our results suggest that worse glycemic control might further increase risk of COVID-19 mortality among those with diabetes. Some studies have also reported that individuals with undiagnosed diabetes are particularly at increased risk of severe COVID-19 infections (3,4). Although relatively few participants had undiagnosed diabetes in the current study, we showed that undiagnosed diabetes was associated with a 3.5-fold excess risk of COVID-19 mortality in men. Although there were no sex differences in the association between HbA_{1c} levels and COVID-19 mortality, the finding that associations are broadly similar across sexes and diseases with the exception of women with CHD is interesting, and it is important when considering mechanistic explanations of the female disadvantage in CHD. Overall, these findings indicate that strategies to prevent diabetes, to promptly identify individuals with diabetes, and to improve glycemic control among those with diabetes could lead to better COVID-19 outcomes for both sexes.

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