Diabetes and COVID-19: Population Impact 18 Months Into the Pandemic

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Eighteen months into the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019 [COVID-19]) pandemic, epidemiologic studies indicate that diabetes is a central contributor to severe COVID-19 morbidity, and, conversely, COVID-19 has had a devastating effect on the population with diabetes. In this literature synthesis, we summarize the relationship of diabetes to COVID-19–related morbidity and mortality, discuss the predictors of severe adverse outcomes and implications of the overall pandemic, and critique the current status of and identify needs for epidemiologic studies for the next phase of the pandemic. Case series show that ∼30–40% of people with COVID-19–related hospitalization, severe morbidity requiring intensive care, and/or death have type 2 or type 1 diabetes. Among hospitalized individuals with diabetes, ∼21–43% required intensive care and case fatality is ∼25%. Risk of severe morbidity and mortality is 100–250% higher among people with diabetes than those without, even after adjustment for sociodemographic factors and comorbid conditions. Impact on the general population with diabetes has been similarly dire, as overall mortality rates were 50% higher than historical trends, a net increase more than twice that of the general population. Of the excess deaths, ∼75–80% are not officially attributed to COVID-19, which raises unanswered questions about missed attribution or collateral impact. Many predictors of poor outcomes have been identified, particularly comorbid conditions (chronic kidney disease, coronary heart disease, and heart failure), concurrent obesity, and acute and chronic poor HbA_{1c} control, that point to the potential to reduce severe morbidity and mortality in its next stages. However, response to the continuing pandemic will benefit from population-wide studies with broader examination of the risks of exposure, infection, and hospitalization, for which few data currently exist. The indirect impact of the pandemic's effects on health services, health behaviors, disease management, care, control, and complications has not been well quantified; determining this impact will be essential to lessen the future impact. Expanding epidemiologic studies of the relationship of diabetes to COVID-19 beyond few high-income countries will also be essential to limit the burden in low- and middle-income countries where 80% of individuals with diabetes reside and where the COVID-19 pandemic has been so damaging.

Barely 1 month following the first reported severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019 [COVID-19]) clusters, diabetes was already identified as an associated factor and key predictor of poor outcomes (1,2). As case series expanded beyond China and were gradually complemented by larger cohorts, the evidence for a central role of diabetes in the COVID-19 epidemic only strengthened, and numerous etiologic links were identified. The potential pathways, including disruption of glucose metabolism, immune

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modulation, coagulation and inflammatory responses; accompanying obesity, cardiovascular disease (CVD), and renal disease; and exacerbation by acute hyperglycemia, could conceivably affect a wide range of outcomes, from COVID-19 risk itself to extensive morbidity and mortality following infection (3–5). In the meantime, understanding the true population-level impact of COVID-19 on diabetes and, conversely, the role of diabetes on the broader course of the epidemic has been slower coming. In this literature synthesis, we summarize the relationship of diabetes to COVID-19–related morbidity and mortality, the predictors of severe adverse outcomes, and implications of the overall pandemic on the population with diabetes. Finally, we critique the status of epidemiologic studies and identify the needs for the next phase of the pandemic.

OVERALL IMPACT OF COVID-19 ON MORBIDITY AND MORTALITY

Quantifying the overall impact of COVID-19 and its subsequent morbidity and mortality is complex because of potential inaccuracies in the attribution of COVID-19, the potential for many indirect effects of the pandemic, and the enormous variation in impact by geography and time. Within 1 year of the pandemic in the U.S., incidence rates of COVID-19 infection ranged from ∼15 per 1,000 per month in its peaks to ∼1.5 per 1,000 per month during its nadirs in the U.S. (6). The global experience also varies considerably. On one end of the spectrum, New Zealand, Vietnam, and Tanzania have logged fewer than 50 deaths, while the U.S., India, Brazil, and Mexico have recorded 200,000–600,000 deaths, representing a 100-fold variation in population incidence rate. Overall case fatality rates among COVID-19 cases are thought to range from 0.5% to 1% (7,8) but vary up to 10-fold across countries, in part due to variation in COVID-19 detection rates (6).

The first wave of the pandemic in the U.S. and U.K. populations was associated with ∼20% net increase in mortality rates, calculated as the difference in overall death rates from any causes relative to historical trends. In the U.K., only World Wars I and II, the 1918 flu epidemic, and the depression of 1929 brought such a dramatic 1-year increase in mortality rates (9). Although global variation in deaths due to COVID-19 has been considerable, the average country toll in excess mortality appears similar to that of the U.S. and U.K. (10,11). In a multicountry study of industrialized countries during the first wave of the pandemic (mid-February to late May 2020), overall death rates were 18% higher than those in previous years.

Of the excess cases, 75–80% were officially attributed to COVID-19 (11–13). The causes of the remaining ∼20–25% not attributed to COVID-19 have not been precisely estimated but are likely some combination of underreporting of COVID-19 and indirect impacts of the pandemic, such as delayed treatment or undertreatment of other conditions causing increases in other causes of death. Meanwhile, some causes of death may have decreased during the pandemic but are obscured within gross mortality estimation. In the U.K., for example, deaths unrelated to COVID-19 in the home and in care homes increased by about half the magnitude of the COVID-19–related deaths, but deaths due to ischemic heart disease, cerebrovascular disease, and ischemic heart disease deaths were ∼10–20% lower than those in the prior year (14).

IMPACT ON THE POPULATION WITH DIABETES

Epidemiologic Methods and Metrics in Studies of Diabetes and COVID-19

To fully understand the epidemiologic relationships of the COVID-19 pandemic, studies would ideally examine risk across a cascade of denominators and outcomes to identify the full range of modifiable risk factors and leverage points for action (Fig. 1). Such a system of data sets or studies would start with the general population as the denominator (Fig. 1, box a) and then consider numerators (Fig. 1, boxes b–g) to estimate incidence rates for exposure, infection, detection, hospitalization, and severe morbidity and mortality (Fig. 1, links B–G). These metrics also identify subpopulations (Fig. 1, boxes b–g) that can serve as the denominators for incremental progression across stages that follow. Such a system would also ideally capture key heterogeneity of the diabetes population, including pediatric

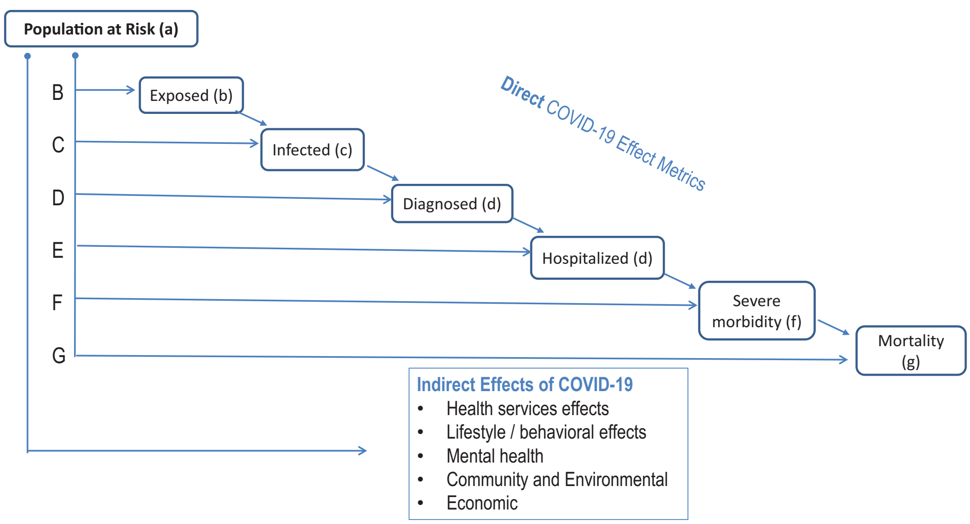

Figure 1—Cascade of metrics for epidemiologic studies to consider in studies of the association of diabetes with direct and indirect outcomes of the COVID-19 pandemic.

populations with type 1 diabetes, as well as potentially exacerbating risk factors in the type 2 diabetes population (obesity, levels of control, concurrent disease).

Due to the combination of the rapid onset of the COVID-19 pandemic and the general data limitations on chronic conditions in reportable disease surveillance systems, the vast majority of studies to date have been case series that use hospitalized individuals with COVID-19 as the sample denominator (Fig. 1, box e) and either severe morbidity (Fig. 1, box f) (e.g., intensive care unit [ICU] admission, need for mechanical ventilation) or 28-day mortality as the outcomes (Fig. 1, box g) (15–17). These studies provide important information related to risk and potential clinical interventions to reduce severe outcomes but are not informative about what affects risk for exposure, infection, diagnosis, or even the hospitalization itself. They also miss adverse outcomes of COVID-19 that develop in individuals who are not hospitalized, as well as outcomes occurring beyond the specific period and measurement of the hospital episode.

Only a few studies have used a full population denominator (Fig. 1, box a), and those have focused on severe morbidity and mortality (18–21). Such population studies have a potential to expand understanding of the contexts of risk factors as well as the range of outcomes. For example, factors related to behaviors, habitation and community context, intrinsic immunity, metabolic control, or local shielding and quarantine policies could differentially affect exposure or infection but only be evident with a population or community denominator. Such studies could also use consider a wide range of "indirect" variables as outcomes, including health behaviors, risk factor management, diabetes-related complications, and morbidity unrelated to COVID-19. Using such data to assess risk at each level of the cascade and to provide relative and absolute risk estimates, proportions affected, population attributable fraction, and trends over time could help shape prevention policies and treatment approaches.

For this review we used the framework shown in Fig. 1 to scope English language epidemiologic studies of the association of diabetes and COVID-19 published through 1 June 2021. We used PubMed, Google Scholar, and international organization websites, using alternative search terms around the central constructs of COVID-19, diabetes, severe morbidity, and mortality (full search strategy available on request). We screened titles and abstracts and analyzed reference lists of relevant articles. Finally, we grouped findings and interpreted studies across three general areas: systematic reviews of cross-sectional studies and case series of diagnosed or hospitalized individuals, longitudinal or population-wide studies assessing diabetes status and COVID-19–related outcomes, and studies of indirect impacts.

Risk of Infection and Hospitalization

A lack of population-based studies of "incidence of infection" or "hospitalization" assessing risk by diabetes status represents one of the most important gaps in the literature. The few reports quantifying diabetes prevalence among uninfected individuals suggest that diabetes is not more common among infected individuals than in the general population, but their representation increases dramatically among hospitalized individuals (23,24). For example, based on the U.S. Centers for Disease Control and Prevention COVID-19-Associated Hospitalization Surveillance Network (COVID-NET), 33% of individuals hospitalized for COVID-19 had diabetes, ranging from 30% to 41% over the year (23) (Fig. 2). By comparison, ∼10% of nonhospitalized individuals in the system's catchment area had diabetes. Diabetes carried a relative risk for COVID-19–related hospitalization of 4.8, and when adjusted for age, sex, and other underlying conditions, a risk ratio of 3.2. A unique longitudinal examination of a registry of over 6,000 individuals who tested positive for COVID-19 from Nashville, Tennessee, found a high cumulative incidence of hospitalization within 14 days of positive test among those with type 1 diabetes (22%) and type 2 diabetes (44%) and found odds three times that of peers without diabetes, with similar magnitude of risk for type 2 diabetes (odds ratio [OR] 3.4) and type 1 diabetes (OR 3.9) after age and other adjustment (24).

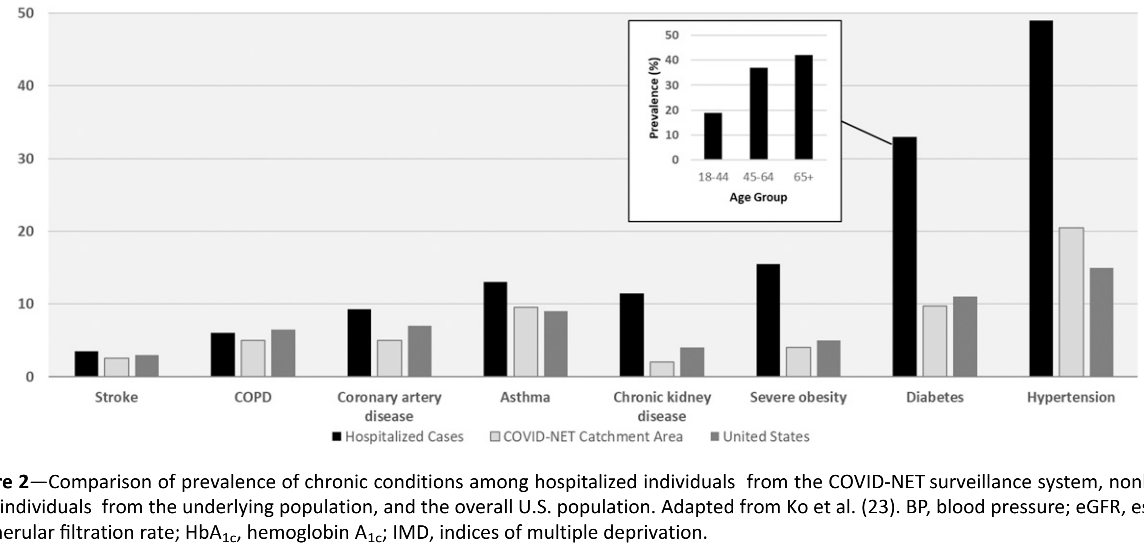

Figure 2—Comparison of prevalence of chronic conditions among hospitalized individuals from the COVID-NET surveillance system, nonhospitalized individuals from the underlying population, and the overall U.S. population. Adapted from Ko et al. (23). BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; IMD, indices of multiple deprivation.

Risk of Morbidity and Mortality Among Hospitalized Individuals

Several systematic reviews of case series have been published, collectively representing dozens of studies (2,15–17, 25–28). Systematic reviews from the first 4 months of the pandemic (December 2019 through March 2020) were dominated by the earliest wave of COVID-19 hospitalizations in China and found a pooled prevalence ranging from 11% to 14.5% (25,29,30). Studies represented by later reviews had greater geographic diversity; reviews incorporating data from the U.S., England, and Middle East found pooled prevalences of 28% and higher (17,28). The prevalence of diabetes is particularly alarming among young and middle-aged adults, reflected in 14 states from the Centers for Disease Control and Prevention COVID-NET, where hospitalized adults aged 50–64 years had a prevalence of diabetes (32%) as high as those aged 65 years and older (31%) (23). Further, a closer examination by Sathish et al. (31) reveals a high prevalence of previously undiagnosed diabetes among persons hospitalized for COVID-19, wherein hyperglycemia and diagnosis may have been precipitated by the COVID-19 infection. This study is a reminder that the degree to which overall prevalence of hospitalized individuals in the systematic reviews reported above are affected by undiagnosed individuals is not clear.

Virtually all of these studies defined their sample denominators as individuals admitted with symptomatic COVID-19, with the most comprehensive review to date assembling 77 standardized studies and >38,000 hospitalized individuals (15,17). On average, 33% of hospitalized individuals with severe COVID-19–related morbidity and 39% of deaths had diabetes. Among individuals with diabetes, 21–43% developed severe disease (i.e., respiratory distress, mechanical ventilation, intensive care unit admission) and case fatality ranged from 24% to 29% (15,17). Studies examining specific treatment outcomes found that diabetes is a potent predictor of the need for invasive mechanical ventilation, extracorporeal membrane oxygenation, and continuous renal replacement therapy (26). Other systematic reviews that assessed associations found ORs of severe disease of 2.4 and death of 2.2 (15) and were noticeably higher among those younger than 55 years (OR = 3.5) (16).

Few data exist on readmission or subsequent sequelae after COVID-19 hospitalization. However, a study of National Health Service hospitals in England found that over an average 5-month follow-up period, 29% of the overall population had a readmission and 5% had a readmission with a diabetes diagnosis. About one-fourth of those readmissions had a new diagnosis of diabetes (32).

Systematic reviews have also compared the prevalence of different comorbid conditions among individuals hospitalized with COVID-19, and their relative risk of COVID-19–related outcomes, finding that prevalence of diabetes (25%) is lower than hypertension (39.5%) and higher than CVD (12%) (17,33). Case fatality rates were similar across individuals with hypertension (28%) and individuals with a smoking history (26%) but notably lower than those for individuals with chronic obstructive pulmonary disease (51%), CVD (52%), chronic kidney disease (48%), and chronic liver disease (39%) (17). ORs for death associated with metabolic and immune system disorders were generally lower (2.5) than those observed for preexisting CVD (3.4), cerebrovascular disease (4.1), and renal disease (3.0) but similar or lower to those in studies examining individuals with cancer and respiratory conditions (2).

Population-Wide Impact of and on Diabetes

Few studies have taken a full population perspective to quantify the relationship of diabetes to COVID-19 (18–22). Two major studies from England and Scotland used health systems data sets to assess the relationship between diabetes and COVID-19–related outcomes in the overall population (18,19). These studies have the advantage of being able to estimate the overall population impact of COVID-19, including the excess risk caused by diabetes, without being biased by the differential risk of hospitalization.

An analysis of a registry of National Health Service practices in England examined risks of in-hospital death with COVID-19 and found a cumulative incidence of 2.6 per 1,000 over a 72-day period in the first wave of the U.K. epidemic (1 March to 11 May 2020) (19), with 31% of the deaths occurring among individuals with diabetes. A similar population-based system from Scotland found a slightly lower incidence (3.6 per 1,000 deaths or critical care unit admission) over a 5-month period that included both the first wave and the early summer when the first wave had receded, while investigators for the OpenSAFELY cohort reported similar estimates of 2.3 per 1,000 over 95 days (20,21).

In multivariate analyses of the English data, including the individuals without diabetes as the referent group, odds of in-hospital COVID-19–related death was 3.5 for indivduals with type 1 diabetes and 2.0 for those with type 2 diabetes, each slightly lower when adjusting for other comorbid factors (OR 2.9 and 1.8 for type 1 diabetes and type 2 diabetes, respectively); ORs were slightly lower in Scotland (OR of 2.4 and 1.4 in individuals with type 2 diabetes and type 1 diabetes, respectively). Material deprivation, male sex, and race/ethnicity (particularly Black, Asian, and mixed) each carried a 50–100% increased odds of death, and comorbid cerebrovascular disease or CVD or heart failure further doubled risk of death. In all these analyses, age was the predominant factor and individuals with diabetes had substantially incre-ased risk across all age strata. However, like most diabetes-related morbidity, the relative risks were highest in younger age strata, as 40-year-olds with type 2 diabetes had an incidence rate 10 times that of individuals without diabetes.

In the English study, the excess mortality relative to historic trends was 51% higher in type 1 diabetes and 64% higher in type 2 diabetes, with about two-thirds of deaths officially attributed to COVID-19 (18,19). As COVID-19–related excess mortality in the general population has been ∼20%, this means that the COVID-19 pandemic waves have had more than twice the impact on the populations with diabetes (20). For additional perspective on how this affected the population with diabetes, these estimates nearing 1 per 1,000 per month represent roughly half of the all-cause death rate for an equivalent period of time in 2018 and are >50% higher than the most common causes of death (vascular diseases and cancers) during a typical equivalent per-iod (34).

PREDICTORS OF COVID-19–RELATED MORBIDITY AND MORTALITY AMONG CASE SERIES WITH DIABETES

A comprehensive systematic review of 22 studies of the predictors of COVID-19 severity and death found male sex, age, several comorbid conditions (CVD, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease), insulin use, and several laboratory predictors on admission, including elevated glucose levels, white blood cell count, neutrophil count, and lymphocyte count to all be significant (18,19, 35–37). Being overweight or obese was associated with ~30% increased risk of severe COVID outcomes but was not associated with mortality. Metformin use tended to be associated with a reduce risk of both COVID-19 severity and death. Of note, diabetes duration, smoking, hypertension, and concurrent cancer were not associated with COVID-19 severity or death among those hospitalized for COVID-19 (36,37)

Figure 3 exemplifies the magnitude of risk associated with significant risk factors for deaths in adults with type 2 diabetes. Age and prevalent chronic kidney disease and CVD (coronary heart disease, stroke, heart failure) have the most glaring increase in absolute risk, ranging from 0.9% to 1.5% of the population over only 72 days (18). These factors each affect 10–20% of the population and have relative risks ranging from 2 to 4. However, male sex, low/normal BMI, Black race, and being underweight/normal weight were each associated with significant increased risks of mortality in multivariate analyses, while current smoking has been surprisingly protective in this and other studies. Scottish data reported a similar range of risk factors for critical care unit admission or death, with age, duration of diabetes, male sex, material deprivation, and comorbid conditions all prominent factors (20).

Determining the degree to which individuals with type 1 diabetes differ from those with type 2 diabetes is difficult because of imprecision of type of diabetes coding as well as the small numbers of individuals that occur in case series. Findings suggest that among adult populations, at any given age, individuals with type 1 diabetes have at least the same risk of poor COVID-19–related outcomes as those with type 2 diabetes (24). However, the case series and population studies described above did not assess the pediatric population, and the degree to which children with type 1 diabetes are at increased risk relative to their peers without diabetes remains unclear (38).

Acute and Chronic Hyperglycemia

Systematic reviews have reported high levels of acute hyperglycemia and a high proportion of undiagnosed diabetes at admission and show that level of fasting plasma glucose on hospital admission for COVID-19 is associated with increased risk of ICU admission and death (31, 39–41). For example, a study of 605 hospitalized individuals from China found that compared with individuals with admission fasting blood glucose (FBG) <6.1 mmol/L, those with FBG 6.1–6.9 mmol/L and FBG ≥7.0 mmol/L had increased risk of in-hospital complications (OR 2.6 and OR 4.0, respectively) within 28 days (39). However, the bidirectional relationship of acute infection and glucose makes it difficult to make conclusions about the degree to which the poor outcomes reflect acute or chronic prior hyperglycemia affecting COVID-19 outcomes or acute hyperglycemia representing a byproduct of the infection itself.

At least three major studies have examined the association of prior levels of HbA_{1c} management and risk of poor outcomes. Population-based studies in both England and Scotland found levels of HbA_{1c} measured months before COVID-19 hospitalization to be associated with risk of ICU admission and/or death, particularly for those with type 1 diabetes. Compared with individuals with a HbA_{1c} of 6.5–7.0, those with an HbA_{1c} of 9.0–9.9 had a 36% higher death rate (18). Similarly, analyses of the UK Biobank found levels of HbA_{1c} to be associated with worse outcomes across the full spectrum of risk, including individuals without diabetes, with newly diagnosed diabetes, and with diagnosed diabetes (42).

The strong association of diabetes with COVID-19 along with the severe hyperglycemia induced by COVID-19

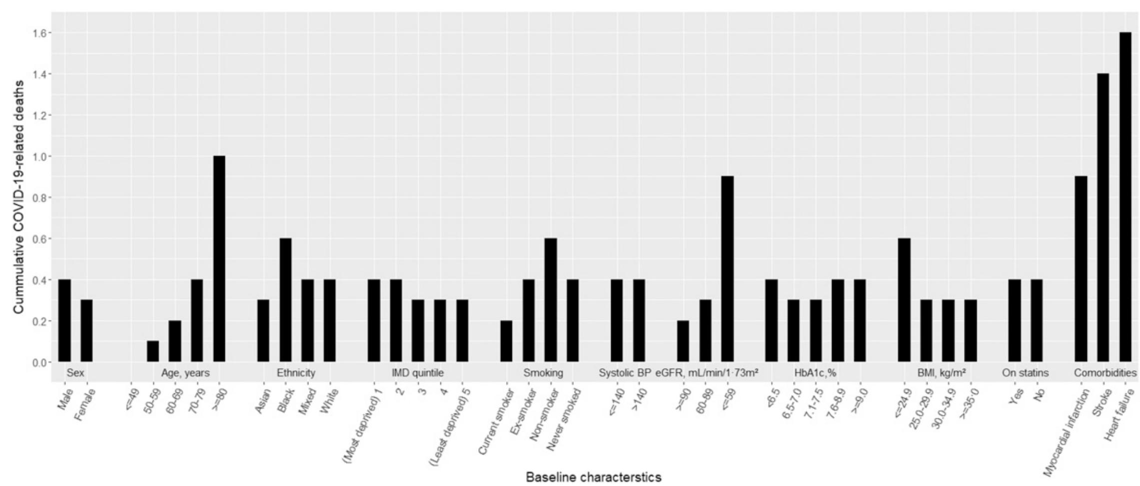

Figure 3—Absolute risk of COVID-19–related mortality among English adults with type 2 diabetes. Adapted from Holman et al. (18). COPD, chronic obstructive pulmonary disease.

infection have raised questions about whether COVID-19 may increase risk for diabetes itself (43,44). The mechanism of such an effect also remains speculative, ranging from ACE2 expression or toxic effects in pancreatic β-cells to autoimmune pathways or effects and insulin resistance acting at muscle or liver. To date, however, the evidence for this comes from case reports but not epidemiologic studies.

INDIRECT IMPACT OF COVID-19 ON THE POPULATION WITH DIABETES

For most people, the most profound effects of the pandemic are not coronavirus infection, but rather the diverse and extended societal disruption the pandemic has caused through changes to health system functioning, behaviors, and community support; environmental changes; or the stress of COVID-19 illness on family members. This disruption could have adverse indirect effects on detection, prevalence, and management of diabetes and other conditions, worsening or improving health behaviors and self-management. Recognizing the indirect effects of the pandemic due to shielding and changes in routines is particularly important for understanding future public health needs for the population with diabetes. Studies examining these indirect impacts are only emerging, and few have examined populations with diabetes.

Health System and Service Effects

The most immediate indirect effects were likely seen in both purposeful and inadvertent redirection of health services (45–47). A population-based study of the primary care practices in England observed a 70% decrease in the rate of diabetes diagnoses and a 30% decrease in HbA_{1c} testing during April 2020; both of these rates gradually returned to usual levels over the subsequent 6 months (47). However, as these trends presumably reflect testing and diagnosis rather than true incidence per se, we may expect a rebound in these rates hereafter. An examination of hospital discharges in England found that compared with those in prior years, rates of minor amputation, major amputation, and lower extremity revascularizations from March through June 2020 were 16%, 28%, and 30% lower, respectively, than in prior years (48). These rates tended to return to typical levels by July, although it may be too early to tell whether these reductions reflected reduced morbidity or deferred treatment that will have delayed effects.

Another analysis of U.K. practice data examined the use of primary care services among individuals with physical and mental health conditions years prior to the pandemic compared with lockdown restrictions in place (45). Across 15 different types of primary care contacts for health conditions, all types except acute alcohol-related event declined, ranging from 6% to 65%, during the initial wave of the pandemic compared with rates of years 2017–2019, gradually returning to typical rates over the course of the year. The largest reduction in the rate of primary care contacts was seen for diabetic emergency (65%), followed by depression and self-harm. It is still unclear whether the reduction in contacts for acute hyperglycemia represents a true reduction in morbidity due to better glycemic management or, alternatively, represents a deferral or neglect of needed care.

The implications of deferring treatments observed in these studies have not been quantified. While some care missed may have been unnecessary there may also be latent adverse effects of deferring care for conditions such as transient ischemic attacks, chronic obstructive pulmonary disease, and asthma, that are realized in later follow-up of health outcomes.

The changes to health services could conceivably influence the management and prevention of a full range of diabetes-related complications. For example, changes to glycemic and blood pressure management could have effects on acute complications and progression of nephropathy and risk of cardiorenal conditions. Reduced detection or early treatment of foot ulcers or access to wound care clinics could increase rates of amputations. However, we are not aware of thorough analyses of these and other specific diabetes-related complications over the past year. Further, the degree to which these changes are specific to the U.K. National Health Service response to the pandemic and represent other countries is unknown.

Health Behaviors

Depending on local policies, the shifts to teleworking from home and closures of or reduced access to grocery stores, restaurants, and fast food could have both short-term or long-term effects on diet quality as well as physical activity habits and diabetes self-management. A scoping review of 23 studies explored the impact of COVID-19 on diet behaviors found that all but 3 studies showed important changes in meal intake (49). The consumption of homemade meals and fruits and vegetables increased but so did intake of comfort food, snacking, number of meals consumed per day, and overall food intake. Other studies found 20–40% increased consumption of sweets (49).

A systematic review of 66 studies examined the impact of COVID-19 lockdowns on physical activity and sedentary behavior (50). Of these studies, 64 observed a change in physical activity; most studies saw a decline in all physical activity and an increase in sedentary behavior but also saw increases in leisure-time physical activity. A meta-analysis found 32% of the general population experiences sleep problems but did not assess changes across the pandemic (51). Finally, an analysis in the U.S. also showed that after the shelter-in-place mandate was implemented, there was a significant increase in weight by about 1.5 pounds per month over a 4-month period (52).

Others have pointed to the potential for indirect effects and unexplained tradeoffs of COVID-19 mitigation policies over much longer time horizons, stemming from diverse factors like delayed cancer treatments, disruption of vaccination programs, drug use and mental health impact, and, in particularly disadvantaged countries, disruption of food and medical supplies (53).

IMPLICATIONS AND PRIORITIES FOR THE FUTURE EPIDEMIOLOGY OF DIABETES AND COVID-19

Summary and Comment

Eighteen months into the COVID-19 pandemic, some countries like the U.K. and U.S. are progressing with vaccination programs and are seeing reduced transmission, serum antibody prevalence, and a more encouraging outlook (6). However, the pandemic continues to reemerge aggressively in other areas, and it is clear that need for strong epidemiologic studies of the intersection between diabetes and

COVID-19 will continue. This literature synthesis highlights the core role that diabetes has in the COVID-19 pandemic and, conversely, the pandemic's impact on the population with diabetes.

The large body of case series tell us that diabetes accounts for 30–40% of severe cases and deaths, and once hospitalized, case fatality is about 25%. Even after adjusting for sociodemographic and health status accompanying diabetes, there is a 100–250% increased risk of poor outcomes. The few population-based absolute incidence rates place COVID-19–related morbidity or mortality among the most common major complications of diabetes (ischemic heart disease, stroke, acute hyperglycemic crisis). Perhaps the most ominous finding has been the 50–64% increase in overall mortality, more than twice the impact seen in the general population. Although yet to be replicated outside the U.K., these findings place COVID-19 in a range similar to that of all vascular deaths or all cancers as a cause of death during the pandemic (33).

Despite the impressive observations of decreased morbidity and mortality, we found the overall epidemiologic literature inadequately narrow to guide clinical and public health decisions and policies for the next stage of the pandemic. Although our synthesis reveals a remarkable dissemination of studies of the association of diabetes and COVID-19 in a short period of time, this evidence base is largely limited to case series of hospitalized cases. These gaps point to four major needs in the epidemiology of diabetes and COVID-19 in the near future.

First, there is a need for studies with population denominators to understand the full cascade of risk referenced in Fig. 1, particularly related to factors underlying exposure, infection, and hospitalization. Such studies are needed to understand whether exposure, infection, and hospitalization risk differ according to diabetes status and how the impact affects health before, outside of, and after hospitalization. These studies are also important to show how behaviors and lifestyle during the pandemic, local shielding and lockdown policies, metabolic and physiologic risk factor control, and household and community context all affect risk.

Second, studies are needed to understand the full range of indirect effects of the pandemic, including factors in care, management, and behaviors that were most dramatically affected, and how these affected health outcomes will be important for upcoming adjustments in the public health response. This will require thoughtfully constructed time series analyses while recognizing the potential for measurement biases. These studies may also identify some unintended benefits of the pandemic resulting from the rapid innovation in care approaches that has occurred.

Third, the pandemic has brought a wealth of natural experiments, for which rigorous examination is needed to understand the effectiveness of the full range of potential interventions to mitigate risk across the full cascade of outcomes. These studies can make use of local and national variation as well as variation over time to understand how behaviors and outcomes were affected. Such studies can take a historical perspective to study prior interventions, as well as current interventions, including how vaccination programs are affecting the population with diabetes. Finally, whole-population studies of the relationship of diabetes to COVID-19–related outcomes are confined largely to the U.K. and U.S. However, 80% of individuals with diabetes reside in low- and middle-income countries with little epidemiologic assessment of the role of diabetes. This leaves the true picture of the relationship and magnitude of diabetes to COVID-19–related outcomes both highly concerning and unclear.

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