Considerations in Epidemiologic Definitions of Undiagnosed Diabetes

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Accurately quantifying undiagnosed type 2 diabetes is an important challenge for conducting diabetes surveillance and identifying the potential missed opportunities for preventing complications. However, there has been little focused attention on how undiagnosed diabetes is defined in epidemiologic surveys and how limitations in methods used to ascertain undiagnosed diabetes may impact our understanding of the magnitude of this important public health problem. This Perspective highlights weaknesses in how undiagnosed diabetes is quantified in epidemiologic research and the biases and caveats that should be considered when using estimates of undiagnosed diabetes to influence public health policy.

In analyses of epidemiologic surveys that include definitions of diabetes using both questions and laboratory tests, respondents who report a prior diabetes diagnosis are classified as having diagnosed diabetes and those who do not report a diagnosis but test positive for diabetes are classified as having undiagnosed diabetes. For decades, this has been the standard practice in studies using data from the Centers for Disease Control and Prevention's (CDC) National Health and Nutrition Examination Survey (NHANES) to estimate undiagnosed diabetes in the U.S. (1–3) as well as population-based data from other U.S. and international studies (4–10). However, there are inherent weaknesses in this epidemiologic definition of undiagnosed diabetes and important implications for its interpretation.

THE OVERESTIMATION OF UNDIAGNOSED DIABETES IN EPIDEMIOLOGIC SURVEYS

Several factors likely lead to an overestimation of undiagnosed diabetes in epidemiologic surveys. Prior research has found that within-person variability in glycemic measures can be high (11–13), leading clinical recommendations to require a confirmation by a second positive test. This intrapersonal variability can be problematic for survey research in which identification of undiagnosed diabetes almost always relies on a single test. An analysis by Selvin et al. (12) of data from an NHANES III substudy found that the prevalence estimates of undiagnosed diabetes as defined by a fasting plasma glucose (FPG) of ≥126 mg/dL would decrease by about 24% if a confirmatory FPG was performed 2 weeks later. This study also found much less within-person variation in A1C, which suggests that the reliability of the definition of undiagnosed diabetes may improve as A1C becomes increasingly used in clinical settings to diagnose diabetes and in epidemiologic surveys to define undiagnosed diabetes. Yet, any requirement for two laboratory tests is going to lower prevalence, as evident in another analysis, which showed that using a combination of both A1C and FPG criteria yielded a 60% lower prevalence than the estimate based on meeting either A1C or FPG criteria (14). However, the "confirmed" definition relied on

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laboratory tests from a single blood sample taken during the same examination visit, and we are not aware of published analyses examining or simulating the real-world process of asking a screened population to return for a second, different glycemic test.

The extent to which undiagnosed diabetes is overestimated in epidemiologic research also depends on the sensitivity of self-report in identifying diagnosed diabetes, a commonly overlooked contributor to error. A considerable number of people who have already been diagnosed but do not report any prior diagnosis may be misclassified or considered as having undiagnosed diabetes (15). How large might this problem be? According to the CDC's 2017 National Diabetes Statistics Report (NDSR 2017) (16), in 2015 there were an estimated 30.2 million adults with diabetes of whom 23.0 million were diagnosed and 7.2 million were classified as undiagnosed. Assuming all adults who have diabetes but who do not report it would test positive for diabetes, we adjusted the estimates of diagnosed diabetes and undiagnosed diabetes for the sensitivity of self-reported diagnosed diabetes. To adjust the number of diagnosed diabetes cases, we divided the estimate of diagnosed diabetes by its sensitivity; to adjust the number of undiagnosed diabetes cases, we subtracted the revised number of diagnosed cases from the total number of cases. These adjustments caused estimates of diagnosed diabetes to increase and estimates of undiagnosed diabetes to decrease. For example, if one assumes an 80% sensitivity, the number of diagnosed adults increased from 23.0 million to 28.8 million and the number of undiagnosed adults with diabetes decreased from 7.2 million to 1.5 million, a 79.9% decrease in undiagnosed cases (Fig. 1). However, if the sensitivity of self-report of diabetes is 95%, the number of undiagnosed cases only decreased by 16.8%. These calculations indicate that the estimated burden of undiagnosed diabetes in the population may be inflated depending on the degree of error in self-reported diabetes. Unfortunately, there have been few population-based studies of the validity of self-reported diabetes, and most of these studies are now dated (15).

Although our Perspective focuses on undiagnosed diabetes, it is worth noting that adjusting diagnosed diabetes estimates for the specificity of self-reported diabetes lowers estimates of diagnosed diabetes and thus total diabetes. For example, adjusting NDSR 2017 estimates for a specificity of 99% to 99.5% would reduce estimates of diagnosed diabetes by ~1–2 million.

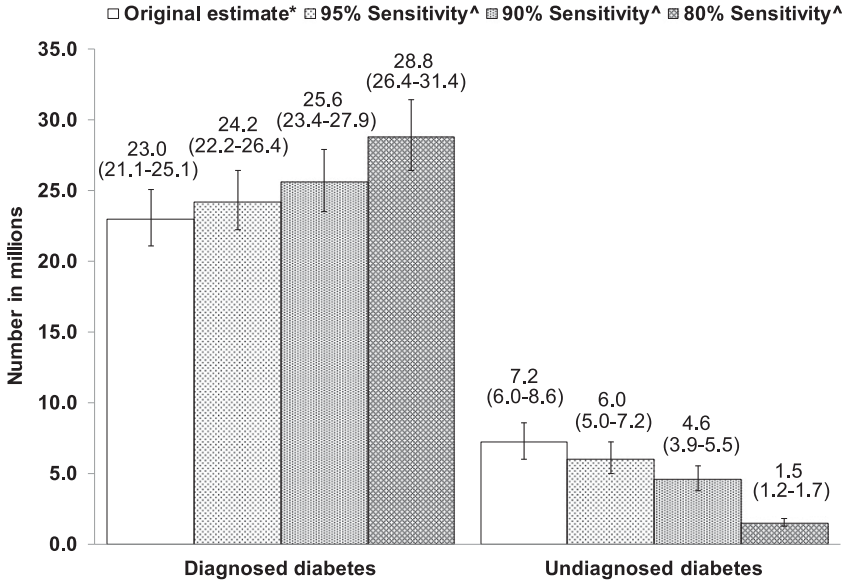

Figure 1—Data are numbers in millions (95% CI). Original (*) and recalculated (^) estimates of the number of U.S. adults with diabetes in 2015. *Original estimates from NDSR 2017. ^Original estimates adjusted by sensitivity of self-report.

CAUTIONS ABOUT INTERPRETATIONS OF UNDIAGNOSED DIABETES ESTIMATES IN EPIDEMIOLOGIC RESEARCH

In addition to the intraindividual variability in glycemic measures and potential bias associated with self-report of diabetes, the magnitude of undiagnosed diabetes can be affected by the type of test used to define a case (17). As shown in Table 1 using 2011–2014 NHANES data for adults, the estimated prevalence of undiagnosed diabetes is greatest when defined by 2-h glucose from an oral glucose tolerance test (OGTT) (3.3%) and least by A1C (1.9%), with FPG falling in between (2.1%). Furthermore, trends in the prevalence of undiagnosed diabetes vary by the test used. As shown in Table 1, among adults aged 40–74 years, there is no monotonic trend in undiagnosed diabetes when defined by A1C, a decreasing trend for FPG between 1988–1994 and 2007–2010, and a decreasing trend for OGTT only since 2003–2006. Further, if care was not taken to use the same test in monitoring trends over time, inaccurate conclusions could be drawn. For example, if one compares the 1988–1994 prevalence of undiagnosed diabetes among adults aged 40–74 years based on an OGTT (6.0%) to the undiagnosed diabetes prevalence in 2011–2014 based on A1C or FPG (2.7%), one might incorrectly conclude that prevalence decreased over 50% between those two time periods.

Changes in laboratory measures can also influence population estimates and trends of undiagnosed diabetes. Such changes, including lack of consistency in laboratory sites, instruments, and measurement methods, have been documented for both A1C and glucose measures over time in NHANES, the main data source for national undiagnosed diabetes estimates (18,19). Adjustments to the data are recommended in some cases to address comparability issues in more recent time periods; however, these calibrations may not be sufficient (14,18–20).

Finally, the proportion of type 2 diabetes that is undiagnosed is often interpreted as an indirect proxy of success in efforts to detect undiagnosed diabetes (3,14,21). However, in epidemiology the concept of "case detection" is classically defined as the ratio of the number of new cases detected to the total number of new cases (detected and undetected) (22). A recent study of epidemiologic

Table 1—Age-standardized prevalence of undiagnosed diabetes, U.S., 1988–2014

Definition	1988–1994	1999–2002	2003–2006	2007–2010	2011–2014
Aged ≥18 years					
A1C ≥6.5%	2.1 (0.1)	1.6 (0.2)	1.7 (0.2)	2.2 (0.1)	1.9 (0.2)
FPG ≥126 mg/dL	2.8 (0.3)	2.7 (0.3)	2.4 (0.3)	2.4 (0.2)	2.1 (0.2)
A1C ≥6.5% or FPG ≥126 mg/dL	3.4 (0.2)	3.1 (0.3)	2.8 (0.3)	3.2 (0.3)	2.7 (0.2)
OGTT ≥200 mg/dL	N/A	N/A	4.7 (0.6)	4.1 (0.3)	3.3 (0.3)
A1C ≥6.5% or FPG ≥126 mg/dL or OGTT ≥200 mg/dL	N/A	N/A	5.1 (0.6)	5.3 (0.4)	4.1 (0.3)
Aged 40–74 years					
A1C ≥6.5%	3.1 (0.2)	2.3 (0.3)	2.3 (0.3)	3.0 (0.2)	2.7 (0.3)
FPG ≥126 mg/dL	4.3 (0.4)	4.0 (0.4)	3.5 (0.5)	2.9 (0.3)	3.0 (0.4)
A1C ≥6.5% or FPG ≥126 mg/dL	5.1 (0.4)	4.4 (0.4)	4.0 (0.6)	4.1 (0.4)	3.9 (0.4)
OGTT ≥200 mg/dL	6.0 (0.6)	N/A	6.6 (1.1)	4.7 (0.5)	4.1 (0.5)
A1C ≥6.5% or FPG ≥126 mg/dL or OGTT ≥200 mg/dL	8.1 (0.7)	N/A	7.4 (1.2)	6.5 (0.6)	5.4 (0.6)

Data are % (SE). A1C ≥6.5%, A1C ≥6.5% (≥48 mmol/mol). 2-h OGTT was only available for those aged 40–74 years for the time period 1988–1994 and was not available (N/A) at all in the time period 1999–2002. For the time period 2003–2006, OGTT was available only for 2005–2006. Estimates were standardized to the 2000 Census population using the following age-groups: 18–44, 45–64, and ≥65 years (for results for ages ≥18 years) or 40–44, 45–64, and 65–74 years (for results for ages 40–74 years).

indices to assess case-finding based on prevalence data demonstrated how the use of the proportion undiagnosed (i.e., diagnosed cases divided by the sum of diagnosed and undiagnosed cases) can yield misleading conclusions and warns against its use; instead, it suggests an alternative measure for case detection based on prevalence data, i.e., the proportion of undiagnosed diabetes among adults without diagnosed diabetes (23). Brinks et al. (23) showed mathematically that this "next-generation" metric is more directly related to the classic definition of case detection. It is also more aligned with the concept of case detection, which seeks to identify people with undiagnosed diabetes from the general population and reclassify them into the diagnosed pool so that preventive action can occur. Although further validation and exploration of the benefits of this metric are needed, this may be the most appropriate indirect index of case-finding (23). The first study to use the new metric showed that among the overall U.S. adult population, detection of undiagnosed diabetes did not increase from 1999 to 2014 (24), whereas previous studies using the standard approach showed more improvements (3,14).

SUMMARY

In this synthesis of contemporary methods and challenges in estimating undiagnosed diabetes and its trend, we make four key points with implications for future measurement and interpretation.

First, both the estimated prevalence and trend of undiagnosed diabetes depend on the type of test used to determine type 2 diabetes status. When comparing and interpreting trends in undiagnosed diabetes prevalence, it is important to ensure that all prevalence estimates are based on the same test.

Second, comparability of glucose and A1C tests should be maintained over time. Stability and alignment of laboratory measurements over time are needed before making inference about undiagnosed diabetes trends.

Third, rather than using the proportion of type 2 diabetes that is undiagnosed, estimating the proportion of undiagnosed diabetes among people without diagnosed diabetes may be a better approach to assess case-finding. If one only has access to prevalence data to monitor trends in detection, then this new metric will be useful in more accurately evaluating the success of diabetes screening efforts (23).

Fourth, within-person variability in glycemic measures and imperfect sensitivity of self-reported type 2 diabetes inflate estimates of undiagnosed type 2 diabetes that are based on typical epidemiologic surveys. The extent to which these factors overestimate undiagnosed diabetes is unknown because *1*) we know little about how diagnoses are made in clinical practice and *2*) there are few population-based studies of the validity of self-reported diabetes. However, our national estimates of undiagnosed diabetes adjusted for the sensitivity of self-reported diabetes suggest that undiagnosed diabetes may be less of a problem than previously thought.

Because of the challenges outlined above, it is important to consider potential biases and degree of uncertainty when using estimates of undiagnosed diabetes to influence public health policy.

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