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ORIGINAL ARTICLE

Estimates of prediabetes and undiagnosed type 2 diabetes in Denmark: The end of an epidemic or a diagnostic artefact?

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Abstract

Background: Up-to-date information on undiagnosed type 2 diabetes and prediabetes based on current diagnostic criteria is lacking. The study aimed to model the total numbers of people with undiagnosed type 2 diabetes and prediabetes in Denmark based on existing population-based surveys. *Methods:* Two population-based Danish studies with information on HbA_{1c}, date of examination, gender, age and known type 2 diabetes were identified: the Danish General Suburban Population Study, n = 21,205, and the Danish Health Examination Survey, n = 18,065. The prevalence of known, undiagnosed and pre-diabetes were estimated in the Danish General Suburban Population Study, and population-level age-specific prevalence of known type 2 diabetes was estimated from national registers. The Danish Health Examination Survey was included for sensitivity analysis. Combining estimates of the survey participation rate among known type 2 diabetes patients with known overall participation rates from the studies allowed for the correction of survey prevalence to plausible population-level estimates of age- and gender-specific prevalence. *Results:* The prevalence of known, undiagnosed and pre-diabetes was highest among men, increasing with age with a peak at age 70. Applying the survey-based prevalence to the entire Danish population, the estimated number (May 2011) with undiagnosed type 2 diabetes was 60,681, corresponding to 24% of all type 2 diabetes cases, and 292,715 had prediabetes, about 50% more than the total type 2 diabetes population. ***Conclusions:*** **Estimates of undiagnosed type 2 diabetes and prediabetes are dramatically lower than reported in previous studies (60,681 vs 200,000 and 292,715 vs 750,000); however, whether this reflects a true decrease in incidence or the change to HbA_{1c}-based diagnostic criteria is not clear.**

Keywords: *Diabetes mellitus, prediabetic stage, prevalence, glycated haemoglobins*

Introduction

Healthcare planning, public health actions and management of type 2 diabetes are dependent on the availability of reliable estimates of prevalence as well as the absolute number of people with prediabetes and type 2 diabetes. In Denmark, prevalence and incidence of diagnosed type 2 diabetes can be monitored using nationwide registers [1]. However, a large proportion of the type 2 diabetes population is asymptomatic and undiagnosed and constitutes a group at high risk of diabetes complications if treatment and complication management is delayed. As no systematic screening for type 2 diabetes and prediabetes is implemented in Denmark, information on the prevalence and absolute numbers with prediabetes and undiagnosed type 2 diabetes can only be obtained from population-based surveys. The most recent estimation employed by the Danish Diabetes Association of the total number of individuals with undiagnosed type 2 diabetes in Denmark is 200,000,

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applying the International Diabetes Federation's (IDF's) assumption of 37.9% of all type 2 diabetes in Europe being undiagnosed [2] to the 320,000 with known type 2 diabetes identified in the former National Diabetes Register (NDR) in 2012 [2,3]. For prediabetes, estimates are based on the Inter99 study from 1999 of adults aged 30–60 [4]; applying these estimates, 750,000 people are predicted to have prediabetes, corresponding to a prevalence of 19% in the entire adult population. The diagnosis of prediabetes in Inter99 was based on an oral glucose tolerance test and included impaired glucose tolerance and impaired fasting glycemia. Several countries such as Denmark, Norway and Germany have adopted haemoglobin A_{1c} (HbA_{1c}) as the recommended diagnostic test for asymptomatic diabetes [5–8]. However, up-to-date information on undiagnosed type 2 diabetes and prediabetes based on current diagnostic criteria is lacking, as are estimates for the entire adult age span. Furthermore, bias may be introduced when estimating type 2 diabetes prevalence from population surveys because people with type 2 diabetes may be less likely to participate in a survey [4]. It is generally known that survey participation is lower among people with disease than those without, leading to an underestimated prevalence of type 2 diabetes and possibly also of undiagnosed type 2 diabetes and prediabetes if survey prevalence was taken at face value. Including unbiased register-based information on diagnosed type 2 diabetes allows in part for the correction for potential participation rate differences between people with and without type 2 diabetes. Thus, the aim of the study was to model the number of people with undiagnosed type 2 diabetes and prediabetes in Denmark by exploiting both existing population-based surveys and register information to correct for differential survey participation between these groups.

Materials and methods

Surveys

Four population-based Danish studies in addition to the Inter99 survey conducted after the year 2000 were identified to explore the representativeness and applicability to model the number of people with undiagnosed type 2 diabetes and prediabetes in Denmark. All surveys had information on HbA_{1c}, date of examination, gender, date of birth (hence age) and known type 2 diabetes. All study participants gave informed consent and all studies were approved by the local ethics committees. All surveys have been carried out in accordance with the principles of the Declaration of Helsinki as revised in 2008.

Identified surveys:

1) The Health2006 survey (H-06): conducted in 2006–2007 in an urban random sample of 3,471 adults from the Capital region, aged 18–69 years. Participation rate: 44.7% [9].
2) The Health2008 survey (H-08): conducted in 2008–2009 in an urban random sample of 3,354 adults from the Capital region, aged 19–72 years without previously known cardiovascular disease, diabetes, chronic obstructive lung disease or other disabilities. Participation rate: 44.0% [10].
3) The Danish Health Examination Survey 2007–2008 (DANHES): conducted from 2007–2008 among 18,065 adults aged 18–90 years in 12 Danish municipalities. Participation rate: 14.0 % [11].
4) The Danish General Suburban Population Study (GESUS): a population-based study from 2010–2014 in a random sample of 21,205 adults aged 25–90 years (20,941 under 85) from Naestved Municipality in Region Zealand. Participation rate: 42.7 % [12].
5) The Inter99 cohort (I-99): conducted in 1999–2001 in a random sample of 6,784 adults from the Capital region, aged 30, 35, 40, 45, 50, 55 and 60 years. Participation rate: 50% [4].

A graphical representation of surveys by age and calendar time is given in Supplementary Figure 1. As the GESUS survey was conducted most recently and comprised the largest age range, the main estimates of undiagnosed type 2 diabetes and prediabetes are based on this survey. The Inter99 was the study underlying the former predicted estimates of undiagnosed type 2 diabetes and prediabetes and as such is presented here, but this survey was not investigated further due to the age of the study and the narrow age range. H-06 and H-08 did not contain sufficient information to warrant prediction of prevalence at the population level and were not sufficiently representative of the age and gender distribution in the background population. Hence only the DANHES study was included, primarily for sensitivity analyses.

Measurements

HbA_{1c} was analysed by ion-exchange high performance liquid chromatography in all studies. In GESUS the analysis was standardized according to the International Federation of Clinical Chemistry (IFCC), whereas HbA_{1c} was aligned to the Diabetes Control and Complications Trial in the other surveys and converted to IFCC standardization for the present study.

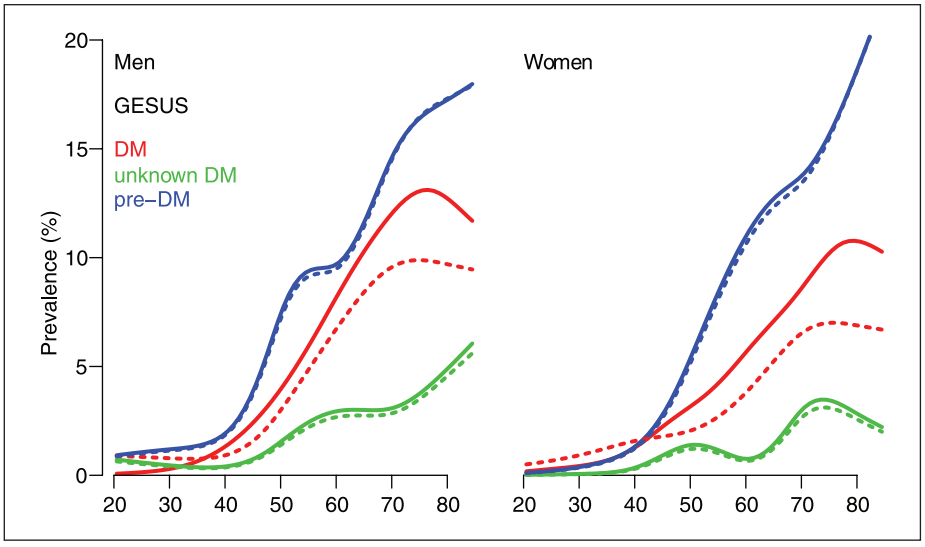

Figure 1. Estimated age-specific prevalence of type 2 diabetes, unknown type 2 diabetes and pre-diabetes in men (left) and women (right) in Denmark in 2011, based on the GESUS study. Median date of survey is 2011.5. Full lines are estimates of the population prevalence and the broken lines are estimates of the survey prevalence (uncorrected) for the three groups. The population prevalence of type 2 diabetes is based on the register data at the median date of survey.

Registers

The former National Diabetes Register in Denmark has not been updated since 2012, so we established a new diabetes register based on validated databases [13]. The following national registers were used to identify individuals with type 2 diabetes: the Danish Register of Medicinal Product Statistics (all filled prescriptions of glucose-lowering drugs since 1995), the Danish National Patient Register (all hospital discharge diagnoses with diabetes since 1977), the Danish Adult Diabetes Database (clinical quality database including type of diabetes since 2005, type 2 diabetes people selected), the Health Services Register (diabetic foot therapy), and DiaBase (clinical quality database of diabetic eye disease since 2013) [14].

Definitions

Known type 2 diabetes in the surveys was defined as self-reported type 2 diabetes or current glucose-lowering medication. Undiagnosed (screen-detected) type 2 diabetes was defined as $HbA_{1c} \geqslant 48$ mmol/mol (6.5%), and prediabetes was defined for HbA_{1c} values in the range 42 mmol/mol (6.0%) to 47 mmol/mol (6.4%) according to Danish guidelines [5].

Diagnosed type 2 diabetes was defined from the registers as the date of the first filed prescription for any antidiabetic drug in Danish Register of Medicinal Product Statistics, date of first diabetes diagnosis in Danish National Patient Registry, date of first diabetes diagnosis in the Danish Adult Diabetes Database, date of first foot examination in the Health Services Register, or the date of the first eye examination in DiaBase, whichever occurred first. People classified with type 1 diabetes in either the National Patient Register or the Danish Adult Diabetes Database are excluded.

Statistical analysis

A core problem in estimating type 2 diabetes prevalence from population surveys is that people with disease – for example, type 2 diabetes – are less likely to participate in a survey. The larger the difference between participation rates among people with and without type 2 diabetes, the more distorted the survey prevalence of type 2 diabetes will be as a representation of population prevalence. By the very nature of a survey, there is no way to estimate the difference in participation rates between people with and without type 2 diabetes, because disease status is only known for the participants, not for the non-participants. This problem will also prevail if people surveyed are not only classified as with diabetes or without diabetes, but as known type 2 diabetes, undiagnosed type 2 diabetes, prediabetes or no type 2 diabetes. However, if we have a source allowing an unbiased estimate of the true population prevalence of type 2 diabetes, then we may use the relationship between the true population prevalence and the survey prevalence to understand the participation rate among people with type 2 diabetes.

Table I. Estimated participation rates (in %) for the two surveys according to prediabetes/diabetes category.

		Known type 2 diabetes	Undiagnosed type 2 diabetes	Prediabetes	Without diabetes	True participation rate
DANHES	Men	7.7	11.1	13.1	14.5	14.0
	Women	7.8	11.0	13.0	14.3	14.0
GESUS	Men	33.9	38.8	41.7	43.7	42.7
	Women	30.9	37.3	41.1	43.6	42.7

DANHES: The Danish Health Examination Survey 2007–2008; GESUS: The Danish General Suburban Population Study.

If we further assume that survey participation increases with decreasing disease severity it will allow a back-calculation to the true population prevalence of undiagnosed type 2 diabetes and prediabetes (Table I).

However, two further assumptions are needed to generate estimates:

1. The ratio of the age-specific participation rates in each group to the total age- and gender-specific participation rates in the survey is independent of age.
2. The participation rate increases in a specific pattern, from type 2 diabetes through no type 2 diabetes; only the slope of this pattern is estimated. Here, we have chosen the relationship between the participation rates in the four groups to be: $(\rho_{T2D};\ \rho_{T2D}+\kappa;\ \rho_{T2D}+1.6\kappa;\ \rho_{T2D}+2\kappa)$, where ρ_{T2D} is the participation rate among type 2 diabetes patients, estimated from the register and the survey, and κ is a parameter estimated from data. In principle we might have chosen a relationship of a different shape (multiplicative for example); the point here is that we reduce the problem to one parameter (κ) that can be solved.

An important input to the algorithm is the 'true' population prevalence of type 2 diabetes; this is derived from a type 2 diabetes register constructed from available Danish health registers as described above. From this we derived age- and gender-specific prevalence (number of cases and total population size) in 1 year age classes as of 1 January 1996–2016. These were modelled by an age-period-cohort model with smooth terms (natural splines), and predictions from this model at the median survey date were used as the 'true' population prevalence in the calculations.

The surveys only reliably cover the age range 20 to 85 years; no information is available beyond 85 years of age. We extrapolated to age 100 by assuming the prevalence of prediabetes and undiagnosed type 2 diabetes declined relative to those at age 85 as did the prevalence of known type 2 diabetes as known from the register.

A detailed exposition of the algorithm used to derive the specific participation rates for people with diagnosed type 2 diabetes, undiagnosed type 2 diabetes, prediabetes and without type 2 diabetes, and a full detailed account of the calculations and statistical analyses, including the R-code deriving results, can be found at http://bendixcarstensen.com/SDC/DF/ESM.pdf.

Results

Figure 1 shows the prevalence of prediabetes, known type 2 diabetes (corrected and uncorrected) and undiagnosed type 2 diabetes by age and gender for the GESUS study. The prevalence of known, undiagnosed and prediabetes was highest among men and increased with age with a peak at age 70. Applying the observed survey prevalence to the entire Danish population aged 20–85 years, the estimated number of individuals with undiagnosed type 2 diabetes by May 2011 was 57,115 corresponding to 24% of the total type 2 diabetes population (32% of the diagnosed type 2 diabetes population); similarly, 271,260 people were predicted to have prediabetes, some 50% more than the estimated diagnosed type 2 diabetes population in this age range at the median survey date of GESUS (n = 178,982). Based on the GESUS survey, Table II shows the number of people in Denmark in the age range 20–85 with known type 2 diabetes, undiagnosed type 2 diabetes, prediabetes and non-type 2 diabetes, and the overall prevalence of these conditions (%). For the sake of completeness, we carried out a sensitivity analysis concerning the relative size of the response rates in people with known type 2 diabetes, undiagnosed type 2 diabetes, prediabetes and without diabetes. Changing the relative difference in response rates from (0.1, 1.6, 2.0) to (0, 1, 2, 3) resp. (0.1, 1.1, 1.2), only changed estimated response rates in undiagnosed type 2 diabetes and prediabetes by 2, respectively 3%, and hardly affected the estimated response rate among people without diabetes. Hence, we used the relative differences fixed at (0.1, 1.6, 2.0) for reporting results.

Estimates based on the DANHES survey were included for sensitivity analysis. Generally, absolute

Table II. Estimated number (*n*) and computed prevalence (in %) among people aged 20–85 years and for 20–100 years in the total Danish population with known type 2 diabetes, undiagnosed type 2 diabetes, prediabetes and no type 2 diabetes, at the median survey dates (DANHES: March 2008; GESUS: May 2011). Results are corrected for differential participation rates between the four groups.

	Known type 2 diabetes		Undiagnosed type 2 diabetes		Prediabetes		Without diabetes		Total Danish population	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
People aged 20–85 years										
DANHES										
Men	81,030	4.1	12,603	0.6	78,190	3.9	1,824,120	90.4	1,995,942	100
Women	67,907	3.3	11,603	0.6	83,672	4.1	1,872,816	92.0	2,035,999	100
Men and women	148,936	3.7	24,206	0.6	161,862	4.0	3,696,936	91.7	4,031,941	100
GESUS										
Men	98,115	4.8	34,765	1.7	135,692	6.7	1,765,450	85.4	2,034,022	100
Women	80,867	3.9	23,943	1.1	135,692	6.5	1,834,449	87.6	2,073,234	100
Men and women	178,982	4.4	57,115	1.4	271,260	6.6	3,599,899	86.5	4,107,256	100
People aged 20–100 years										
DANHES										
Men	84,083	4.1	14,131	0.7	83,040	4.1	1,846,910	91.1	2,082,163	100
Women	74,204	3.5	13,165	0.6	96,704	4.6	1,926,861	91.3	2,111,026	100
Men and women	158,377	3.8	27,297	0.7	179,744	4.3	3,773,771	91.2	4,139,188	100
GESUS										
Men	101,923	4.9	36,738	1.8	141,551	6.8	1,788,860	86.5	2,069,073	100
Women	88,275	4.1	23,943	1.1	151,163	7.0	1,887,860	87.8	2,150,505	100
Men and women	190,199	4.5	60,681	1.4	292,715	6.9	3,675,983	87.1	4,219,577	100

DANHES: The Danish Health Examination Survey 2007–2008; GESUS: The Danish General Suburban Population Study.

numbers and prevalence are slightly lower in the DANHES survey compared to GESUS, although they display similar patterns across age groups and a similar relationship between prediabetes, undiagnosed and known type 2 diabetes, partly because the reference is to the median dates of the surveys: March 2008 for DANHES and May 2011 for GESUS.

Discussion

In addition to the 180,000 people aged 20–85 years with diagnosed type 2 diabetes in Denmark (as of May 2011) identified in updated registers, we estimated that some 57,000 people in Denmark have undiagnosed type 2 diabetes, corresponding to 24 % of all type 2 diabetes for this age range. This number is markedly lower than previous projections of 200,000 people with undiagnosed type 2 diabetes, corresponding to ~40% of all diabetes (all ages) in 2012 in the NDR. This may be explained by different factors. Firstly, improved diagnostic activity over the last decade may give rise to a smaller undiagnosed-to-diagnosed type 2 diabetes ratio. Studies such as the Inter99 [4] and the Addition Trial [15] have substantially increased the awareness of undiagnosed diabetes in Denmark. Secondly, the relative contribution of undiagnosed type 2 diabetes may decline simply if the number of people with prevalent type 2 diabetes increases due to declining mortality among people with diagnosed type 2 diabetes. Thirdly, a change in diagnostic criteria from the oral glucose tolerance test to HbA_{1c} has been shown to markedly reduce the size of the population with diabetes [16,17]. This could explain the lower number of people with known and undiagnosed type 2 diabetes but should not necessarily affect the proportion of undiagnosed type 2 diabetes relative to diagnosed type 2 diabetes. Finally, although studies have demonstrated that the Danish NDR overestimated the numbers of people with type 2 diabetes [18], applying the fixed estimation of 37.9% undiagnosed cases according to the IDF assumption [2], the overestimation itself would successively infer a false large absolute predicted number of undiagnosed type 2 diabetes.

We predict that 271,260 people have prediabetes (May 2011) when applying data from the population survey GESUS to the total Danish population for people aged 20–85 years. A bold extrapolation to age 100 gives 292,715. These numbers are considerably lower than previous estimates of 750,000 people (all ages) defined by impaired fasting glycemia and impaired glucose tolerance based on the oral glucose tolerance test. Based on the current data it is not possible to disentangle whether the change in diagnostic criteria or a true decline in underlying risk factors for type 2 diabetes explain this discrepancy. Generally, there is little evidence underlying the suggested thresholds for the HbA_{1c}-defined definition of prediabetes,

and most evidence on the risk of progression to and prevention of type 2 diabetes is based on studies of people classified by impaired glucose tolerance rather than HbA_{1c} [19–21].

The current study provides the most recent estimates of type 2 diabetes (diagnosed and undiagnosed) and prediabetes in Denmark based on a large population-based study covering a broad age range. Lack of representativeness is the main limitation, particularly for H-08 (by design) and DANHES (potential selection bias due to low participation rate), so the DANHES study was included in the final analysis primarily for sensitivity purposes. Although HbA_{1c} measurements were standardized to both The Diabetes Control and Complications Trial (DCCT) and IFCC, differences in methods for the analysis of HbA_{1c} across surveys may have influenced the estimates; however, it is not possible to determine the direction (let alone magnitude) of such potential bias. Unfortunately, Oral Glucose Tolerance Test (OGTT) data were not available in the studies to enable comparison between the different diagnostic criteria. However, although the study aimed to estimate the absolute burden of disease based on current diagnostic criteria, a comparison of methods was not its purpose as such. Finally, although selection biases due to differences in participation across diabetes and prediabetes groups seem less important, regional and socioeconomic differences between the studied populations and the general Danish population may still play a role. Unfortunately, we had no access to individual-level information on geography and socioeconomic status. The main strength of our study relates to the use of unbiased register data for the validation of estimates of undiagnosed type 2 diabetes and prediabetes relative to known type 2 diabetes in the surveys to compensate for potential selection bias. Other strengths of the study relate to the thorough modelling of known and undiagnosed type 2 diabetes and prediabetes taking differences in participation rates into account, and that we obtained broadly comparable results from the primary survey and the cohort included for sensitivity analysis despite dramatically different overall participation rates.

To our knowledge, no European studies have been published during the last 10 years on type 2 diabetes and prediabetes based on HbA_{1c} [22]. It thus remains unknown whether the reduction in undiagnosed type 2 diabetes observed in Denmark applies to other countries, or whether this apparent improvement may be explained by the use of HbA_{1c} as a diagnostic parameter, requiring only non-fasting measures in place of the cumbersome oral glucose tolerance test. Our results question whether the IDF assumption about 37.9% undiagnosed type 2 diabetes can be applied in all countries, and consequently whether it may overestimate the total number of people with type 2 diabetes.

The large proportion of undiagnosed type 2 diabetes has been the primary argument for systematic screening for type 2 diabetes in the population. However, the evidence for an effect of type 2 diabetes screening is not strong and most screening programmes have not been able to capture high-risk individuals with sufficient specificity. Our results indicate that diagnostic activity has improved with earlier detection of patients with type 2 diabetes, thus questioning the need for systematic screening in the population. However, according to our data, some 24% of all cases are still undiagnosed, so algorithms to identify high-risk individuals might be useful to resolve the remaining problem.

We conclude that the estimates of the numbers of individuals with undiagnosed type 2 diabetes and prediabetes in Denmark are markedly lower than suggested by previous studies, even after correcting for differential survey participation. The results underline the importance of regular representative population surveys of type 2 diabetes. It is not clear whether this reflects a true fall in incidence, improved diagnostic activity or the change to HbA_{1c}-based diagnostic criteria in 2011. Unfortunately, no incidence data from the follow up of cohort studies are available to support or deny these hypotheses. However, a decline in incidence in other countries seems to have occurred in parallel to employment of new HbA_{1c}-based diagnostic criteria in 2012 [23–25], indicating a role of the diagnostic criteria themselves. A recent Danish study showed that the prevalence of long-term complications at the time of diagnosis [26] is roughly unchanged compared to studies conducted in the 1990s. Whether this indicates a loss of sensitivity to detect complications early or improved specificity leaving out cases at low risk of complications using HbA1c instead of the OGTT remains unknown and should be evaluated carefully in follow-up studies.

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