Changes in type 2 diabetes incidence and mortality associated with introduction of HbA1c as diagnostic option: A Danish 24-year population-based study

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Summary

Background In 2011, the World Health Organization began recommending glycated haemoglobin (HbA_{1c}) as a measure for diagnosing type 2 diabetes (T2D). This initiative may have changed basic T2D epidemiology. Consequently, we examined time changes in T2D incidence and mortality during 1995-2018.

Methods In this population-based cohort study, we included 415,553 individuals with incident T2D. We calculated annual age-standardized incidence rates of T2D. We examined HbA_{1c} testing and used Poisson-regression to investigate all-cause mortality among the T2D patients and a matched comparison cohort from the general population over successive 3-year periods.

Findings From 1995 to the 2012 introduction of HbA_{1c} testing as a diagnostic option in Denmark, the annual standardized incidence rate (SIR) of T2D doubled, from 193 to 396 per 100,000 persons (4.1% increase annually). From 2012 onwards, the T2D incidence declined by 36%, reaching 253 per 100,000 persons in 2018 (5.7% decrease annually). This was driven by fewer patients starting treatment with an HbA_{1c} measurement of <6·5% or without prior HbA_{1c} testing. Mortality per 1,000 person-years following a T2D diagnosis decreased by 44% between 1995-1997 and 2010-2012, from 69 deaths to 38 deaths (adjusted mortality rate ratio: 0·55 (95% CI: 0·54-0·56)). After the low level during 2010-2012, mortality increased again by 27% to 48 per 1,000 person-years (95% CI: 46-50) by 2016-2018.

Interpretation Our findings suggest that introducing HbA_{1c} as a diagnostic option may have changed basic T2D epidemiology by leaving patients undiagnosed, that previously would have been diagnosed and treated.

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INTRODUCTION

The estimated global type 2 diabetes (T2D) prevalence has increased from 108 million adults in 1980 to 422 million in 2014.[1] It is predicted to nearly double by 2030-2045,[2,3] but any projections are sensitive to developing trends in incidence of T2D and changes in mortality rates.

Diagnosis of T2D has traditionally relied on either fasting blood glucose (FBG) measurements or 2-hour oral glucose tolerance tests (OGTT).[4,5] More convenient and robust diagnostic options have been pursued for decades, and in 2011 the World Health Organization concluded that glycated haemoglobin (HbA_{1c}) measurements could be used for T2D diagnosis, as an alternative to the two established diagnostic methods. It furthermore concluded there was insufficient evidence to make any formal recommendation on the

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Research in Context

Evidence before this study

There is now evidence from several high income countries in Europe and North America that the growth in diabetes prevalence has subsided and the incidence has begun to decrease. Recent landmark studies in the US and Scandinavia showed that all-cause mortality among adults with type 2 diabetes (T2D) has continuously declined until the late 2000s where it almost were approaching general population mortality. In 2011 the World Health Organization concluded that glycated haemoglobin (HbA_{1c}) measurements could be used for type 2 diabetes diagnosis, co-existing with fasting blood glucose, and 2-hour oral glucose tolerance testing. There is limited overlap between which patients are diagnosed using the different testing options, and any impact of introducing HbA_{1c} as de facto diagnostic method upon T2D population incidence and prognosis is poorly understood.

Added value of this study

From 1995 to the 2012 introduction of HbA_{1c} testing as a diagnostic option in Denmark, the annual standardized incidence rate (SIR) of T2D doubled (4.1% annual increase). From 2012 onwards, the T2D incidence declined by 36% in 2018 (5.7% annual decrease). The decline was driven by a reduced number of patients who started glucose-lowering treatment with an HbA_{1c} measurement below the new diagnostic threshold of <6·5% or without a previous HbA_{1c} measurement. All-cause mortality following a T2D diagnosis decreased by 44% between 1995-1997 and 2010-2012. After the low level of mortality during 2010-2012, mortality increased again by 27% by 2016-2018. This was driven by an increase in mortality during the first year following T2D diagnosis.

Implication of all the available evidence

Our findings suggest the introduction of HbA_{1c} as diagnostic option may have changed basic T2D epidemiology by leaving patients, that previously would have been treated, undiagnosed. We may thus be missing a group with borderline increased HbA1c values that is still at high metabolic risk and might benefit from a global cardiovascular risk assessment. These findings may have implications for clinical practice and suggest that a more multifactorial view of metabolic risk is needed.

interpretation of HbA_{1c} levels below 6.5%.[4] However, in a screening study in primary care, HbA_{1c} testing only identified 48% of those who were diagnosed with diabetes based on FBG or OGTT.[6] Similarly, screening people with coronary heart disease for diabetes using both FBG, OGTT and HbA1c revealed that only 7% were diagnosed by all three methods.[7] Nevertheless, HbA_{1c} testing may have become the predominantly used diagnostic tool after a 2012 update of diagnostic recommendations by health authorities.[8-10] There is now evidence from several high income countries in Europe and North America that the growth in diabetes prevalence has subsided and the incidence has begun to decrease.[11] The impact of the recent introduction of HbA_{1c} testing on both diabetes incidence and mortality is poorly understood. Studies from Denmark and other countries noted declining T2D incidence after the introduction of HbA_{1c} testing as a diagnostic option, but generally lacked a combination of longitudinal HbA_{1c} testing data and T2D incidence data to further explore the role of HbA_{1c} testing.[12-15] Other recent studies included too few years after the introduction of HbA_{1c} measurements for T2D diagnosis to reliably evaluate any impact on diabetes incidence.[14–17] Recent landmark studies in the US and Scandinavia showed that all-cause mortality among adults with T2D has continuously declined until the late 2000s where it almost approached general population mortality.[18,19] However, the newest trend curves indicate that excess mortality from diabetes may have begun to rise again after the time of diagnostic HbA_{1c} introduction.[18-20]

We aimed to investigate temporal changes in incidence and all-cause mortality among patients with incident T2D during 1995-2018. We compared these trends to mortality trends in the general population and examined the consequences of introducing HbA_{1c} as a diagnostic option in 2012.

METHODS

Study design, setting, and participants

We conducted a population-based longitudinal study covering the entire population of Denmark (5·8 million inhabitants) based on national healthcare data for 1990-2018. All analyses involving HbA_{1c} tests were limited to the population residing in Northern Denmark (1·8 million inhabitants), where these data were available. The Danish national healthcare system provides universal tax-supported healthcare, guaranteeing unfettered access to general practitioners and hospitals, and partial reimbursement for prescribed drugs. The unique personal civil registration number assigned to all Danish residents at birth or upon immigration allows for unambiguous linkage of data sources at the individual level.[21]

Data sources

We linked four existing population-based medical databases in our study.[21] The Danish National Prescription Registry covers all prescriptions redeemed at any pharmacy in Denmark since 1994.[21] The Danish National Registry of Patients (DNRP) contains data on dates of admission and discharge from all Danish non-psychiatric hospitals since 1977 and records of emergency and

outpatient specialist clinic visits since 1995.[21] Each hospital encounter is recorded in the DNRP with one primary diagnosis and potentially multiple secondary diagnoses and since 1994 coded using the *International Classification of Diseases, Tenth Revision* (ICD-10). The Clinical Laboratory Information System (LABKA) database contains laboratory results from tests ordered in primary care practices and hospitals in Northern Denmark from 1990 onwards.[21] The Danish Civil Registration System (CRS)[21] was established in 1968 and provides daily updates on the age, sex, vital status, and residency of all inhabitants. [21]

Diabetes patients and general population comparators

Starting in 1995, we identified patients with incident T2D using either the date of their first-ever redemption of a glucose-lowering drug prescription (Anatomical Therapeutic Chemical classification system [ATC] code starting with A10) or the date of their first ever DNRP hospital contact with a diagnosis of diabetes or a diabetes complication (ICD-8 or ICD-10 codes starting with 249-250, 2515, E10-E15, O24, T383A, M142, G590, G632, H280, H334, H450, H360, N083), whichever occurred first. The applicable date was defined as the diabetes diagnosis date in our study. We excluded patients who had not resided in Denmark for at least one year prior to this date. To ensure inclusion of truly incident patients, we excluded those who were diagnosed with diabetes or redeemed any glucose-lowering drug before 1 January 1995. Patients who were diagnosed with diabetes or redeemed insulin before age 30 years (ATC code starting with A10A) or any glucose-lowering drug before age 15 years were excluded as likely having type 1 diabetes.[22] Women who gave birth within nine months after a diabetes diagnosis were excluded as likely having gestational diabetes mellitus. Women who had pre-existing hospital diagnosed polycystic ovarian syndrome or who redeemed any metformin prescription (ATC code A10BA02) in combination with clomifen (ATC code G03GB02) within 12 months following a diabetes diagnosis were excluded as likely having polycystic ovarian syndrome. Some patients with other forms of diabetes, e.g. type 1 diabetes diagnosed in late adulthood at age 30+ years, latent autoimmune diabetes in adults (LADA), or rare monogenic diabetes types, were thus categorized as having type 2 diabetes in our study. On the T2D diagnosis date, we matched each patient with five comparators from the general Danish population based on age (year of birth) and sex, defining the patient's first treatment date as the index date of that patient's comparators. Comparators were subject to the same exclusion criteria as patients with diabetes.

Comorbidities and mortality

We used the DNRP to obtain information on any comorbid conditions included in the Charlson Comorbidity Index (CCI),[21,23] registered within five years prior to or on the diagnosis/index date. We categorized the severity of comorbidity using the CCI score (excluding diabetes), adapted for use with hospital discharge data.[23] We computed the total CCI score for each individual, defining four categories of comorbidity: a total score of 0 (no comorbidity), a total score of 1 (moderate comorbidity), a total score of 2 (severe comorbidity), or a total score of ≥ 3 (very severe comorbidity). The CRS was used to link data on all-cause mortality and migration status of each patient and comparator until the end of 2018.[21]

HbA_{1c}

For each patient in Northern Denmark with available laboratory data, the latest available HbA_{1c} measurement within one year before first T2D treatment was obtained from the LABKA database. We used the following values to categorize baseline HbA_{1c} levels: no measurement available, <6·5%, 6·5-6·9%, 7·0-7·4%, 7·5-7·9%, 8·0-8·9%, 9·0-9·9%, and ≥10%.[24]

Statistical analysis

We first compiled descriptive characteristics for all T2D patients according to 3-year periods of diagnosis. To assess changes in incidence of T2D over time, we plotted standardized incidence rates (SIRs) of T2D for each year, standardized to the age and sex distribution of the population of Denmark in 2012. Next, we restricted the population to Northern Denmark where laboratory data were available and calculated and plotted incidence rates (IRs) of T2D associated with different baseline HbA_{1c} categories. We modelled the incidence rates for all T2D patients by calendar year using a Poisson model. This was done separately for the periods separated by HbA_{1c}'s introduction as a diagnostic option (1995-2011 and 2011-2018).

To evaluate temporal changes in all-cause mortality among incident T2D patients, for each calendar year we calculated and plotted the all-cause mortality risk during 365 day intervals: 0-1 years, 1-2 years, 2-3 years, 3-4 years, and 4-5 years after first T2D treatment, separately for men and women and age-standardized to the incident T2D population in 2012. Next, we followed T2D patients and their population comparators from the diagnosis/index date until death, migration, first T2D diagnosis (in comparators), or end of follow-up, whichever came first. We plotted the cumulative unadjusted mortality by year of diagnosis. We used a Poisson regression model to plot mortality rates per 1,000 person-years for T2D patients and comparators, using all available follow-up time (maximum 24 years). We then examined changes in all-cause mortality rates for 3-year periods, using the first period, 1995-1997, as the reference period and calculating mortality rate ratios (MRR) adjusted for changes over time in age, sex, and

comorbidity (continuous CCI score). We plotted annual changes in diabetes incidence by age categories and mortality for diabetes patients and comparators. In a sensitivity analysis, we repeated the mortality rate ratio calculations replacing the Poisson model with a Cox regression model. In another sensitivity analysis we excluded all patients diagnosed using ICD-10 code E14 "other diabetes" (v n = 4,493), patients initiating insulin monotherapy between 30 and 40 years of age (n = 3,303), patients with pre-existing pancreatic disease (n = 3,148), and patients redeeming at least one glucocorticoid prescription 12 month prior to diagnosis (n = 35,135).

Role of the funding source
The study was funded by Aarhus University. The funder had no influence on any of the following: study design, analysis, interpretation, writing of the report or decision to submit the paper for publication.

RESULTS

Patient characteristics
We identified 415,553 patients treated for T2D in Denmark for the first time from 1995 through 2018 and 2.060.279 matched comparators. For each 3-year period, baseline characteristics of the T2D patients at date of first treatment are presented in Table 1 and those of the comparators are presented in Table S1. Median age was 62·9 years (IQR: 52·9-72·5 years). We followed the T2D patients for a total of 2·7 million person-years. Median age at first T2D treatment fell from 63·7 years in 1995-1997 to 61·6 years in 2016-2018, while the sex distribution saw increasingly more men (55% to 57% male). The proportion with hospital-diagnosed comorbidity CCI score ≥2 increased from 14% to 28% during the study period. Median pre-treatment HbA_{1c} values among T2D patients decreased substantially, from 8·7% in 1995-1997 to 7·0% in 2016-2018. A low median HbA_{1c} level of 6·7% occurred in 2010-2012, when 25% of the patients (=lower quartile) had an HbA_{1c} measurement of less than 6·3% (i.e., below the current diagnostic HbA_{1c} threshold) at treatment initiation (Table 1).

Incidence
From 1995 to the 2012 introduction of HbA_{1c} as a diagnostic option, the annual SIR of T2D per 100,000 people more than doubled from 193 to 396 (4.1% annualized increase). From 2011 to 2018, the annual SIR declined by 36% to 253 per 100,000 persons (Figure 1: **top panel**), with an overall low seen in 2014 (5.7% annualized decrease). The SIRs increased for men and women in all age groups until 2011, but the subsequent decline was predominantly observed in the older age groups (Figure 1: **middle panel, and Figure S2: lower panel)**. Thus, in the age group ≥60 years, both men and women experienced a >50% decline in diabetes incidence from 2011 to 2014 (Figure 1: **middle panel and Figure S2: middle panel)**. The decline in incidence was almost entirely driven by a reduction in the number of patients who started treatment with an HbA_{1c} measurement below the new diagnostic HbA_{1c} threshold of 6·5% or without a previous HbA_{1c} measurement (Figure 1: **bottom panel and Figure S4)**. After the 2014 low, the incidence increased more in men than in women **(Figure S2: top panel).**

Mortality
The all-cause mortality risks within 0-1 years, 1-2 years, 2-3 years, 3-4 years, and 4-5 years after first treatment were similar in men and women with T2D (Figure 2). The mortality risk within 0-1 year was clearly higher than subsequent one-year mortality risks. The 0-1 year mortality also showed the greatest variability over time, when findings before and after the diagnostic change in 2012 were compared (Figure 2). The adjusted mortality rate per 1,000 person-years among T2D patients decreased by 44%, from 72 deaths per 1,000 person-years during the reference period 1995-1997 to 40 deaths per 1,000 person-years during 2010-2012 (adjusted MRR: 0·55 [95% CI: 0·54-0·56]) (Table 2). After the low level of mortality in 2010-2012, mortality increased again by 27% to 48 per 1,000 person-years (95% CI: 46-50) during 2016-2018, corresponding to an adjusted MRR of 0·69 compared to the reference period 1995-1997 (Table 2). The reverted mortality trend after 2010-2012 was caused almost entirely by an increase in 0-1 year mortality (Figure 2). **Figure S5** shows the annual mortality rates for T2D patients versus population comparators, adjusted by Poisson regression for age (60 years), sex (male), and comorbidities (CCI score 0). During 17 consecutive years before 2012, T2D mortality rates gradually converged between T2D patients and population comparators (**Figure S5**). In the following six years (until 2018), rates diverged again, caused by an increase in mortality in T2D patients and a continued decrease in mortality in the general population (Table 2, **Figure S5**). **Figure S6** shows the successively decreasing cumulative mortality in T2D patients until 2010-2012 and increasing mortality hereafter. **Figure S7** shows that the proportion of patients diagnosed with type 2 diabetes that had received an OGTT or FBG test quickly decreased after the 2011 introduction of HbA1c as a diagnostic test. **Figure S8** shows that the year-to-year percentage changes in type 2 diabetes incidence and mortality were relatively stable until 2011, after which their variability increased much. **Figure S12** shows that trends were generally similar across age groups.

	Period of diagnosis 1995-1997 N (%)	1998-2000 N (%)	2001-2003 N (%)	2004-2006 N (%)	2007-2009 N (%)	2010-2012 N (%)	2013-2015 N (%)	2016-2018 N (%)
Overall	34790	40068	46948	53897	61182	71653	51680	55328
Sex								
Male	19,036 (55)	22,297 (56)	26,132 (56)	29,338 (54)	33,713 (55)	39,920 (56)	29,120 (56)	31,777 (57)
Female	15,754 (45)	17,771 (44)	20,816 (44)	24,559 (46)	27,469 (45)	31,733 (44)	22,560 (44)	23,551 (43)
Age (years)								
<50	6,730 (19)	7,100 (18)	8,379 (18)	10,577 (20)	12,089 (20)	12,764 (18)	10,130 (20)	11,511 (21)
50-59	7,600 (22)	9,715 (24)	11,526 (25)	12,338 (23)	13,208 (22)	15,522 (22)	11,656 (23)	13,722 (25)
60-69	8,265 (24)	9,718 (24)	11,995 (26)	14,462 (27)	17,687 (29)	21,728 (30)	14,075 (27)	14,052 (25)
70-79	8,024 (23)	8,680 (22)	9,489 (20)	10,430 (19)	11,874 (19)	14,529 (20)	10,428 (20)	11,223 (20)
80+	4,171 (12)	4,855 (12)	5,559 (12)	6,090 (11)	6,324 (10)	7,110 (10)	5,391 (10)	4,820 (9)
Median (IQR)	63.70 (52.50, 74.00)	63.40 (53.30, 73.70)	62.70 (53.60, 73.20)	62.40 (52.90, 72.60)	62.70 (52.80, 71.90)	63.60 (53.70, 72.10)	63.00 (52.50, 72.10)	61.60 (51.80, 71.40)
Comorbidity								
No comorbidity	24,951 (72)	27,813 (69)	31,951 (68)	36,151 (67)	39,762 (65)	44,840 (63)	30,576 (59)	32,813 (59)
Moderate	4,990 (14)	6,040 (15)	7,188 (15)	8,179 (15)	9,016 (15)	10,296 (14)	7,008 (14)	7,037 (13)
Severe	3,005 (9)	3,674 (9)	4,460 (9)	5,138 (10)	6,191 (10)	7,487 (10)	5,502 (11)	5,847 (11)
Very severe	1,844 (5)	2,541 (6)	3,349 (7)	4,429 (8)	6,213 (10)	9,030 (13)	8,594 (17)	9,631 (17)
HbA_{1c} (%)*								
No measurement	9,032 (86)	8,333 (70)	7,524 (54)	6,931 (43)	4,899 (25)	2,966 (13)	992 (6)	588 (3)
<6•5	165 (2)	616 (5)	1,448 (10)	2,534 (16)	4,088 (21)	7,054 (30)	3,992 (24)	3,415 (19)
6•5-6•9	113 (1)	418 (3)	821 (6)	1,343 (8)	2,727 (14)	5,775 (24)	4,970 (30)	5,834 (33)
7-7•4	138 (1)	366 (3)	750 (5)	1,283 (8)	2,424 (13)	2,750 (12)	1,956 (12)	2,336 (13)
7•5-7•9	119 (1)	343 (3)	628 (5)	916 (6)	1,390 (7)	1,333 (6)	1,033 (6)	1,156 (7)
8-8•9	254 (2)	599 (5)	911 (7)	1,131 (7)	1,392 (7)	1,460 (6)	1,232 (7)	1,408 (8)
9-9•9	225 (2)	427 (4)	590 (4)	694 (4)	806 (4)	782 (3)	787 (5)	847 (5)
≥10	447 (4)	842 (7)	1,181 (9)	1,301 (8)	1,581 (8)	1,542 (7)	1,610 (10)	1,954 (11)
# measurements Median HbA_{1c} (IQR)	1,461; 8.70 (7.30, 10.40)	3,611; 8.00 (6.80, 9.80)	6,329; 7.60 (6.50, 9.20)	9,202; 7.20 (6.40, 8.60)	14,408; 7.00 (6.40, 8.00)	20,696; 6.72 (6.30, 7.46)	15,580; 6.91 (6.45, 7.82)	16,950; 7.00 (6.54, 7.91)
First diagnosed using hospital diagnosis data n (%)	14,679 (42)	17,265 (43)	20,497 (43)	20,931 (39)	19,096 (31)	16,345 (23)	13,059 (25)	10,601 (19)
First diagnosed using prescription data n (%)	20,118 (58)	22,803 (57)	26,441 (57)	32,967 (61)	42,095 (69)	55,308 (77)	38,617 (75)	44,731 (81)

***Table 1*: Sex, age, comorbidity, and HbA_{1c} values of type 2 diabetes patients in Denmark, by period of diagnosis.**
Categories of comorbidity were based on Charlson Comorbidity Index (CCI) scores of 0 (no comorbidity), 1 (moderate), 2 (severe), and ≥3 (very severe); Diabetes was excluded from the CCI score. 30,233 (7.2%) of patients with incident diabetes had not redeemed a glucose lowering prescription before ultimo 2018.

* HbA_{1c} results are limited to persons who resided in Northern Denmark at the time of their T2D diagnosis.

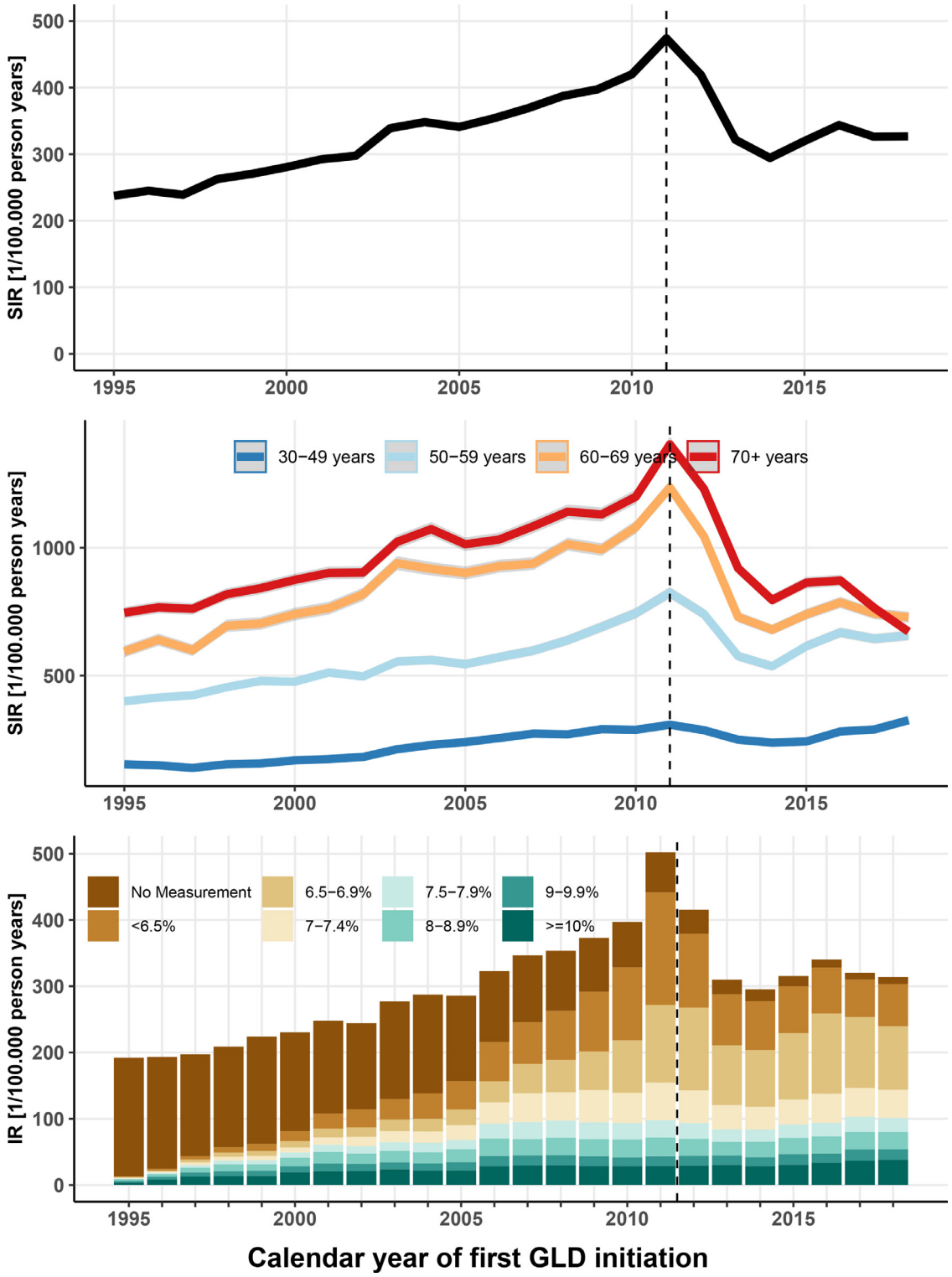

Figure 1. The top panel depicts age- and sex-standardized incidence rates (SIRs) among patients with incident type 2 diabetes with 95% confidence intervals by year of diagnosis. Similarly, the **middle panel shows** SIRs by age categories. The **bottom panel** shows the incidence rate stratified by baseline HbA_{1c} measurement at time of first treatment among type 2 diabetes patients living in Northern Denmark at time of diagnosis. Incidence trends in this regional setting are similar to those on a national level.

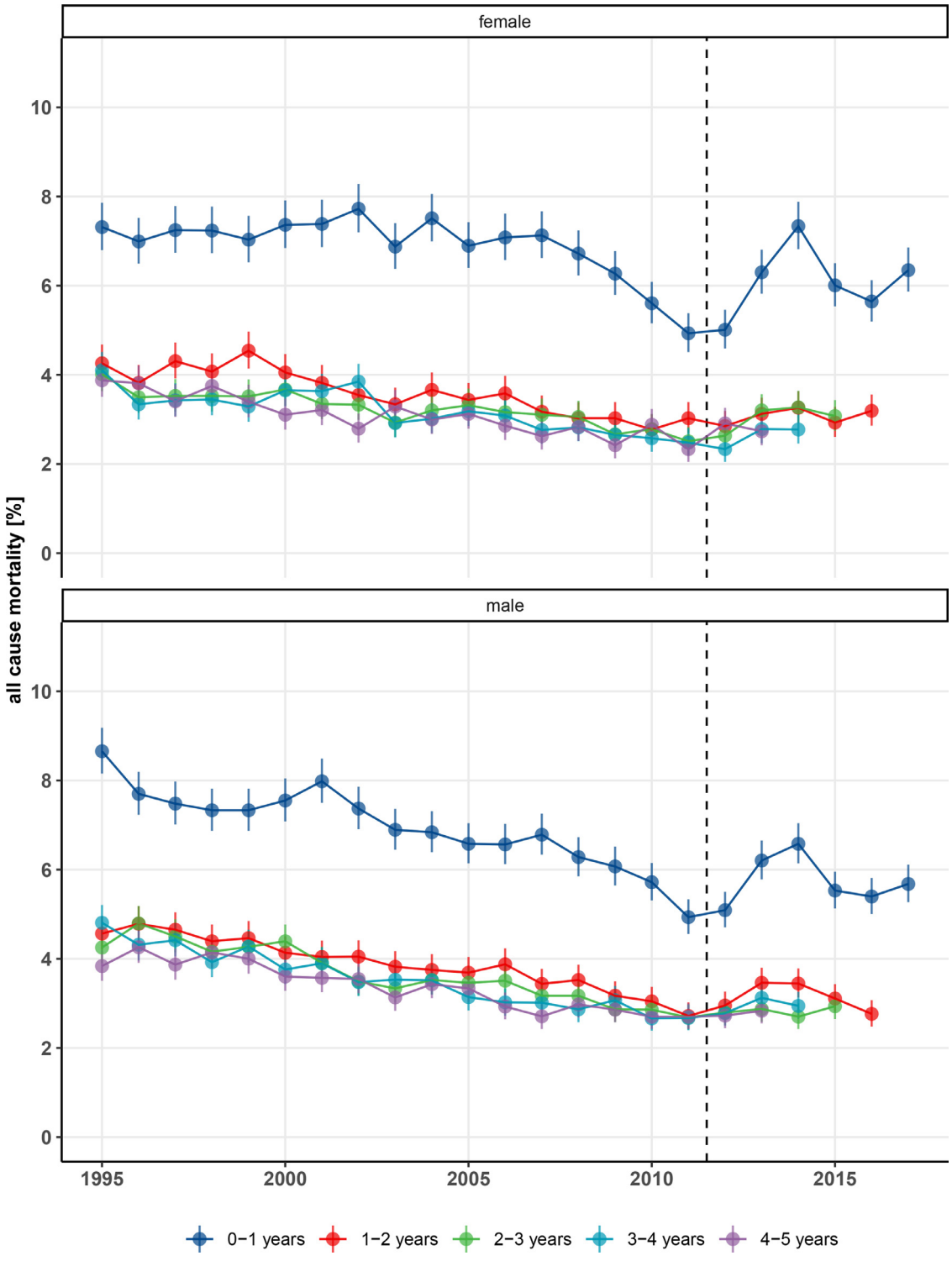

Figure 2. Age-standardized all-cause mortality by year in men and women with type 2 diabetes treated for the first time, Denmark, 1995-2018.

Period of diagnosis	Persons N	Type 2 diabetes patients					Comparators				
		Risk time (years)	Events N	Mortality Rate/ 1000 py	rate ratio (95% CI) – crude	rate ratio (95% CI) – adjusted*	Persons N	Events N	Mortality Rate/ 1000 py	rate ratio (95% CI) - crude	rate ratio (95% CI) – adjusted*
1995-1997	34790	441244	24992	69.49 (67.31-71.73)	1 (1-1)	1 (1-1)	172546	89778	35.69 (35.04-36.35)	1 (1-1)	1 (1-1)
1998-2000	40068	484218	25779	64.05 (62.06-66.12)	0.94 (0.92-0.96)	0.92 (0.91-0.94)	199171	89779	33.96 (33.34-34.58)	0.93 (0.93-0.94)	0.95 (0.94-0.96)
2001-2003	46948	530348	25432	57.73 (55.93-59.59)	0.85 (0.83-0.86)	0.83 (0.82-0.85)	233371	87018	32.55 (31.96-33.15)	0.85 (0.85-0.86)	0.91 (0.9-0.92)
2004-2006	53897	544638	23378	52.63 (50.97-54.34)	0.76 (0.74-0.77)	0.76 (0.74-0.77)	267430	78797	30.26 (29.71-30.83)	0.77 (0.76-0.77)	0.85 (0.84-0.86)
2007-2009	61182	519800	19920	45.46 (44-46.96)	0.68 (0.66-0.69)	0.65 (0.64-0.67)	303373	65827	27.19 (26.68-27.7)	0.68 (0.68-0.69)	0.76 (0.75-0.77)
2010-2012	71653	467392	16264	37.98 (36.73-39.27)	0.61 (0.6-0.63)	0.55 (0.54-0.56)	355366	53872	24.15 (23.68-24.61)	0.63 (0.62-0.64)	0.68 (0.67-0.68)
2013-2015	51680	208681	8536	41.68 (40.17-43.25)	0.72 (0.7-0.74)	0.6 (0.58-0.62)	255866	22602	21.1 (20.65-21.57)	0.58 (0.57-0.59)	0.59 (0.58-0.6)
2016-2018	55328	80428	3727	48.08 (46-50.26)	0.82 (0.79-0.85)	0.69 (0.67-0.72)	273121	7419	19.33 (18.78-19.89)	0.5 (0.49-0.52)	0.54 (0.53-0.55)

Table 2: **Mortality rate and mortality rate ratios over time for T2D patients and age- and sex-matched comparators.**

* Adjusted for age, sex and comorbidity. Abbreviations: py, person years; CI, confidence intervals.

DISCUSSION

We observed a doubling of the incidence of T2D in Denmark between 1995 and 2011, when HbA_{1c} was first introduced as a primary diagnostic method. During the same period, mortality following first T2D dianggnosisgnosis was halved. Between 2012 and 2018, we found a marked decline in T2D incidence, driven by fewer elderly patients and fewer patients with a baseline HbA_{1c} of <6·5%. In parallel, T2D mortality rates climbed back to pre-2012 levels. These results suggest that the shift to using HbA_{1c} measurements as a diagnostic tool has had an important impact on diabetes incidence rates. In relation to estimating current diabetes mortality, it is important to note that the shift to HbA_{1c} testing may have changed the character of the denominator, selecting a treated diabetic population at higher risk. Precise estimation of the direction of the T2D epidemic may require inclusion of laboratory data in the consideration of case definitions.

Comparison with other studies

Our population-based study used 24 consecutive years of data to examine associations between HbA_{1c} measurements, T2D incidence, and all-cause mortality. The continuously increasing incidence and improving prognosis of T2D that we observed during the 2000s accords with findings from previous US,[19,25] Norwegian,[15] Swedish,[17,18] Finnish,[26] Danish,[27-29] UK,[30-31] Portuguese[32] and Australian[33] studies.[11] Most of these studies were based on T2D data from before the introduction of HbA_{1c} measurements for diagnostic purposes[25,26,33,34] or included only few data points following this change,[14-19,30,32] hampering assessment of subsequent changing in trends. A recent multi-country analysis suggested that the incidence of diagnosed diabetes is now stabilising or declining in many high-income countries.[14] That study concluded that the reasons for the declines in the incidence of diagnosed diabetes warrant further investigation with appropriate data sources, which was a main objective of our study. We were unable to identify other similar population-based incidence studies that included long-term time trends of HbA_{1c} levels at diagnosis. A recent Norwegian study reported declining T2D incidence during 2009-2014, similar to our findings, but did not include information on HbA_{1c} levels or T2D mortality. In the US, where using HbA_{1c} measurements for diagnosis was introduced as early as in 2010, a decline in T2D incidence began a few years earlier than observed in our study,[12] indicating that reductions in T2D incidence might be partly caused by the introduction of HbA_{1c} as a diagnostic option. A recent study from Denmark covering the period 1996-2016 similarly found that T2D incidence increased until 2011, declined until 2014, but seems to increase again after 2015.[28] Our findings through 2018 corroborate and extend these results.

With few exceptions,[30] previous studies have reported evolving mortality time trends among prevalent, not incident, T2D patients. A recent study from Denmark reported recently declining mortality among patients with prevalent T2D[28] which includes mostly T2D patients diagnosed before the diagnostic changes in 2012. The population with prevalent T2D is important because it reflects the patient mix that most doctors see in everyday clinical care. The specific mortality rate in incident T2D patients is also important, and we are adding this evidence in our study. Several other studies comparing mortality trends in prevalent T2D patients versus general population comparators reported a convergence in mortality rates among T2D patients and comparison subjects in the years prior to the introduction of HbA_{1c} as a diagnostic test,[18,19,31] which corroborates our findings. A Swedish population-based study found that a continuous decline in all-cause mortality in prevalent diabetes patients began to reverse in 2010-2011, while mortality rates continued to decrease in matched controls.[18] This is also in line with our findings. A UK study similarly reported all-cause mortality increases in T2D patients from 2012 to 2014, in contrast with a continued decline among controls.[31] A US study based on the National Health Interview Survey reported a continuous T2D mortality decrease between 1988-1994 and 2010-2015, but pooling of the most recent years may have masked recent changes in mortality trends.[19] Authors of previous studies that suggested increasing T2D mortality trends in most recent years generally abstained from commenting on the trends, possibly because too few data points were available to make an unambiguous assessment of the increases in mortality.

Strengths and limitations

We conducted a population-based cohort study in a setting with uniform access to health care, complete registration of hospital admissions, drug prescriptions, and laboratory data, and complete follow-up until death or emigration. This reduced selection biases stemming from selective inclusion of, e.g., specific hospitals, health insurance systems, or age groups.

Several limitations should be considered when interpreting our findings. Increased screening for T2D and earlier initiation of glucose-lowering drugs following T2D diagnosis[35] would tend to temporarily inflate increases in T2D incidence, introducing a lead time bias resulting in apparent decreased mortality. There was high screening activity and a focus on early detection and intensive glucose control promoted by diabetes associations during the 2000s, which was then somewhat offset following the 2008 publication of the ADVANCE trial[36] and a more conservative treatment approach. These mechanisms could offer an alternative hypothesis for the apparently transient increase and then fall in T2D incidence. In turn, during the 2010s new cardiology guidelines on HbA1c screening in patients with cardiovascular disease could have led to inclusion of a subgroup of more severely ill T2D patients than in the earlier years. This perhaps contributed to the trend of increased short-term mortality that we observed in the 2010s.

In addition, we could only identify and follow patients from the date of their first glucose-lowering drug treatment or first diabetes related hospital contact and had no means to assess T2D patients exclusively treated with changes in diet and lifestyle. Thus, in theory, trends could be affected by changes in clinicians' decisions about whether or when to initiate pharmacological therapy. In the mid-2000s, the focus on early intensive T2D therapeutic intervention in primary care increased and the "watchful waiting" and solely diet/lifestyle change approaches declined. Accordingly, T2D individuals were increasingly more likely to be captured by community pharmacy prescription databases as the primary (first) data source from the mid-2000s, rather than being captured in hospital diagnosis databases first. The proportion first diagnosed using prescription data increased from 58% (1995-1997) to 81% (2016-2018). Since the vast majority of registered T2D individuals would be captured in both data sources after a shorter or longer delay, usually within the first years after diabetes registration,[37] we do not believe these factors to cause major bias in incidence trends over time. We do not consider this a bias per se in our prognosis study, as earlier detection and initiation of therapy can be considered causal factors in the improvement of T2D prognosis over time. Still, recent data indicate that 15-18% of all diabetes patients known in primary care may not receive medical treatment and may not be captured by the included data sources,[38] which is an inherent limitation of our study.

Some patients tested with HbA_{1c} may still have been diagnosed with FBG. This study did not include complete information on FBG, HbA_{1c} and OGTT, because tests from general practitioners analysed locally e.g. by use of point-of-care diagnostics are not included in the LABKA database. We did however examine trends in OGTT and FBG testing on the available data in order to address this limitation. We found sharp declines in the use of both tests following 2012 (**Figure S7**). We were able to adjust for changes in comorbidity during a period of 24 years, using diagnoses recorded in the DNRP (previously validated with positive predictive values exceeding 90%) and included in the CCI. Still, improved ascertainment of comorbidities over time may have contributed to more complete comorbidity adjustment in recent years and thus to an overestimation of mortality improvements compared with earlier years.

Generalizability, implications, and conclusions

The observed trends in T2D epidemiology in Denmark may apply to other high-income countries with similar

trends in lifestyle risk factors and similar changes to T2D diagnosis and therapy guidelines in recent decades. It is made clear in recent guidelines that the HbA_{1c} test is just one among several T2D diagnostic options aiming at identifying patients at increased risk of complications. These tests still include both OGTT testing and FBG testing. Nonetheless, HbA_{1c} testing is clearly the most convenient method for patients and physicians in everyday clinical practice, as it requires no fasting and planning, has less day-to-day variability and causes less discomfort. Of note, all three options for T2D diagnosis and their thresholds have been validated by their ability to predict diabetic retinopathy, rather than mortality.[4] There is currently much discussion about the fact that a considerable proportion of T2D patients may fulfil the diagnostic requirements of one method, but not the others.[7] Patients diagnosed by different T2D diagnostic methods may represent different disease phenotypes or stages and thus have a different prognosis.[39] In accordance with previous observations,[6] our findings suggest that a significant proportion of incident T2D patients, with blood glucose in the diabetic range but normal (or pre-diabetic) HbA_{1c} values of <6·5%, remained undiagnosed and untreated after 2012. In effect, this indicates that reported declines in T2D incidence may be an artefact resulting from a new diagnostic option. If that is the case, we might expect a later compensatory increase in T2D incidence when initially untreated T2D patients experience further increases in blood glucose and HbA_{1c} values and are eventually diagnosed. Indeed, we observed a return to a trend of increasing T2D incidence, particularly in men, in the most recent years. However, more data are needed to evaluate whether this trend is transient.

The dramatic decline in registered T2D incidence starting in 2012 coincided with increasing early T2D mortality, possibly because increased use of HbA_{1c} testing removed T2D patients with hyperglycemia but normal or pre-diabetic HbA_{1c} values (and potentially better short-term prognosis) from the pool of treated T2D patients. One could argue that an increase in average T2D mortality with removal of anticipated "lower-risk" patients was expected when introducing HbA_{1c} for T2D diagnosis. This might constitute an important healthcare problem only if these individuals have a materially elevated risk of cardiovascular events and death versus other individuals,[40,41] and would have likely benefitted from T2D diagnosis and treatment.[42] Of note, many individuals with prediabetes and diabetes have other metabolic disturbances and cardiovascular risk factors,[18,42] regardless of the diagnostic definition for diabetes. There are good tools to quantify global cardiovascular risk, such as the recently revised SCORE equation.[43] A recent regression discontinuity design study found that individuals with an incident HbA_{1c} measure just *above* the T2D treatment threshold of 6·5% experienced a 21% *lower* rate of death or cardiovascular event than those with an HbA1c just below the threshold, indicating that patients with HbA_{1c} just below the threshold are indeed a vulnerable patient group that might benefit from a global cardiovascular risk assessment and multifactorial treatment.[44]

In conclusion, we found that the incidence of T2D doubled while T2D mortality nearly halved between 1995 and 2011. After the 2012 shift in diagnostic policy, we saw a marked decline in T2D incidence and a higher mortality, probably driven by a shift in the case-mix of diagnosed T2D patients and fewer patients with a baseline HbA_{1c} of <6·5% initiating T2D treatment. Our findings suggest that fewer patients have been diagnosed with T2D since HbA_{1c} testing was introduced as a convenient diagnostic option. We may thus be missing a group with borderline increased HbA_{1c} values that is still at high metabolic and cardiovascular risk.[44] These findings may have implications for clinical practice and suggest that a more multifactorial view of metabolic risk is needed.

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Ethics approval: Not needed for purely registry-based studies in Denmark.

Patient involvement

Patients were not involved in posing the research question, choosing the outcome measures, or in the design or implementation of the study. There are no plans to involve patients in the dissemination of the results.

Data sharing: Due to restrictions related to Danish law and protecting patient privacy, the combined set of data as used in this study can only be made available through a trusted third party, Statistics Denmark. This state organisation holds the data used for this study. University-based Danish scientific organisations can be authorized to work with data within Statistics Denmark and such organisations can provide access to individual scientists inside and outside of Denmark. Requests for data may be directed to Statistics Denmark: forskningsservice@dst.dk or +45 39 17 31 32.

Transparency: The senior author, RWT, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanepe.2021.100291.

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