Diabetes mortality differs between registers due to various disease definitions

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ABSTRACT

INTRODUCTION: We evaluated the impact of including haemoglobin A_{1c} (HbA_{1c}) measurements in a regional algorithm for identification of diabetics by comparing the population identified by the regional algorithm with diabetics registered in the National Danish Diabetes Register (NDR) relative to prevalence, co-morbidity and five-year mortality rate.

MATERIAL AND METHODS: The regional (County of Vejle) and national diabetes populations were compared per the inclusion date of 31 December 2006 limited to persons residing in four municipalities in the County of Vejle, Denmark.

RESULTS: A total of 14,998 diabetics were identified by the regional algorithm, of whom 11,499 (prevalence 4.1%) resided in the four municipalities. The total number of diabetics registered in the NDR was 227,621 in Denmark, of whom 10,976 (prevalence 4.0%) resided in the four municipalities. The regional diabetics (2,802 persons) not identified in the NDR population had a significantly lower mortality rate (57%) than the diabetics (2,279 persons) in the NDR population not identified by the regional algorithm.

CONCLUSION: The significantly higher mortality in the NDR population not identified by the regional algorithm may stem from differences between the components of the two algorithms, i.e. frequency of glucose measurements in the NDR versus frequency of HbA_{1c} measurements including elevated values in the regional algorithm. The NDR algorithm, which includes the use of frequency of glucose measurements without a value over the diagnostic threshold, identified about 21% of persons who probably had their glucose measured for other reasons than diabetes.

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The National Danish Diabetes Register (NDR) was introduced in 2006 and aims at including all Danish citizens with known diabetes [1] to assess long-term trends in the incidence, prevalence and mortality from diabetes. The NDR offers opportunities for research into the epidemiological and public health aspects of diabetes by record linkage with other Danish health registers using the unique personal identification code (CPR number) assigned by the Danish Civil Registration System to all Danish citizens.

Before the establishment of the NDR, a system for the identification of diabetes patients in the former County of Vejle was established in order to monitor concentrations of haemoglobin A_{1c} (HbA_{1c}) as an intermediate outcome of the quality of health care [2, 3]. To investigate the epidemiological characteristics of diabetes in the former County of Vejle, we established the regional algorithm including abnormal values of HbA_{1c} as one of its criteria. We hypothesised that using abnormal HbA_{1c} values would be the correct way of identifying patients with diabetes. The hypothesis was based on our previous findings and on the work of Kristensen et al [4] in which the sensitivity and positive predictive value (PPV) for abnormal HbA_{1c} were high.

The aim of this work was to compare the diabetes population of the former County of Vejle as identified by the regional algorithm, including frequency and abnormal HbA_{1c} values, with the diabetes population identified using the national algorithm of the NDR. The populations were compared with respect to prevalence, co-morbidity (using the Charlson Index [5]) and the five-year mortality rate.

MATERIAL AND METHODS

Identification of candidate diabetics in the former Vejle County – regional population

Prior to the Danish structural reform which created new administrative units as of 1 January 2007, the former County of Vejle had a population of 360,921 inhabitants, corresponding to 6.6% of the Danish population. From this population, candidate diabetics were identified from regional registers using the following algorithm (**Table 1**):

Source I: The County Laboratory Database (LABKA): Patients registered with at least one HbA_{1c} value ≥ 6.6% in the period from January 1996 to December 2006 from the four hospital laboratories (Vejle, Kolding, Fredericia, Horsens) and general practice within the former County of Vejle.

Source II: LABKA: Patients registered with at least three HbA_{1c} measurements with a value < 6.6% over the years from January 2002 to December 2006 from the above-mentioned sources.

ORIGINAL ARTICLE

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TABLE 1

Specification of the criteria in the national and regional algorithms, respectively, and number of subjects identified. Included: subjects residing in the new municipalities 607, 615, 630 and 766 as of December 31, 2006 (effective from January 1, 2007).

Source specification	National algorithm of the National Danish Diabetes Register: Danish Health and Medicines Authority	Regional algorithm: Vejle County	Subjects identified by, n: national algorithm	regional algorithm	joint[a]
The National Danish Patient Register	ICD8: 249, 250 ICD10: DE10, DE11, DE12, DE13, DE14, DO24, DH360	ICD8: 249[b], 250 ICD10: DE10, DE11, DE12[b], DE13[b], DE14[b] (Source IV)	6,512	6,369	6,229
The National Danish Prescription Register	≥ 2 prescriptions included in the ATC codes A10A (insulin) and/or A10B (peroral antidiabetic drugs) redeemed within a period of 6 months	≥ 1 prescription included in the ATC codes A10A (insulin) and/or A10B (peroral antidiabetic drugs) within the period from Jan 2006 through Dec 2006 (Source III)	7,199	7,242	6,939
The National Danish Health Service Register	Referrals to chiropody for diabetes	NA	4,033	NA	NA
	Blood glucose measurements: ≥ 2 measurements annually over 5 consecutive yrs	NA	1,719	NA	NA
	Blood glucose measurements: ≥ 5 measurements within a period of 1 yr	NA	7,348	NA	NA
The County Laboratory Database	NA	≥ 3 measurements of HbA_{1c} within the period Jan 1996 through Dec 2006 (Source II)	NA	9,575	NA
	NA	≥ 1 vales of HbA_{1c} ≥ 6.6% within the period Jan 1996 through Dec 2006 (Source I)	NA	8,150	NA
Total			10,976	11,499	8,697

ICD = International Classification of Diseases; NA = not applicable.
a) Identified by both algorithms; b) Supplementary search for these codes performed in 2011.

Source III: The Danish National Prescription Register (DNPrR): Patients registered with at least one prescription handled in the former County of Vejle in the period from 1 January 2006 through 31 December 2006 for anti-diabetics with the Anatomical Therapeutic Chemical Classification System (ATC) [6] code A10A (insulin) and/or A10B (oral anti-diabetic agents).

Source IV: The Danish National Patient Register (LPR): All patients registered with a contact (inpatient-based and outpatient-based) in the period from 1977 through December 2006 at hospitals in the former County of Vejle with a diabetes diagnosis (International Classification of Diseases (ICD) codes 249 and/or 250 (Eights Revision) or codes DE10, DE11, DE12, DE13 and/or DE14 (Tenths Revision) [7].

The study population was limited to persons who were alive and residing in the former County of Vejle on 31 December 2006 according to the CPR register.

Identification of candidate diabetics using the NDR – national population

Inclusion into the NDR takes place when a person is first-time registered in one of five possible ways, based on data in the LPR and in the DNPrR as well as registrations with blood glucose measurements and diabetes-specific chiropody codes (Table 1 further described in [1]).

Comparison of the regional diabetes population with the National Danish Diabetes Register population

For descriptive and comparative analyses, we included all subjects identified by the regional algorithm and/or by the NDR who were alive as of 31 December 2006 and who resided in one of the four new municipalities of Fredericia (code 607), Horsens (code 615), Vejle (code 630) or Hedensted (code 766). These four municipalities combined can be mapped correctly from part of the former County of Vejle to part of the new Region of Southern Denmark.

Candidate diabetics identified by the national algorithm of NDR without being identified by the regional population (Reg) (i.e. NDR+&Reg-) and candidate diabetics identified by the regional algorithm without being identified in the NDR population (NDR-&Reg+) as well as those identified by both algorithms (NDR+&Reg+) were compared with regard to ascertainment methods, comorbidity expressed using the Charlson Index score [5], and five-year mortality rate as well as age distribution.

Charlson Index

The Charlson Index (CHI) is the sum of contribution from 19 groups of diagnoses [5, 8]. The CHI was established for each study person by a search in the diagnosis codes for all contacts in the LPR registered in the ten-year period leading up to 31 December 2006. Co-morbid conditions included in the CHI were counted only once in the period for each patient, and we excluded diabetes diagnosis codes from contributing to the CHI. The final CHI score was grouped into CHI score = 0, CHI score 1-2, CHI and score ≥ 3 and, finally, the two last groups were merged into CHI score ≥ 1.

Five-year mortality rate

All deaths in both the regional and the NDR diabetes populations during the five-year period were obtained from the CPR register and person-years at risk were calculated for each subject from 31 December 2006 until the date of death, the date of moving out of the study area or until 31 December 2011, whichever came first. The five-year mortality rate was calculated by dividing the total number of deaths by the total number of person-years for the national and regional population as well as for the NDR+&Reg-, NDR-&Reg+ and NDR+&Reg+, respectively.

Statistical analyses

To compare NDR+&Reg- with NDR-&Reg+ concerning categorical variables, Pearson's χ^2-test was used.

The limits of the confidence intervals (CI) around the mortality rates were estimated as suggested in [8].

To control for the potential confounding effect of age in the comparisons of the distribution of the CHI and the five-year mortality rates in the two contrasting populations, NDR+&Reg- and NDR-&Reg+, respectively, a Mantel-Haenszel analysis [9] was used with stratification according to males and females as well as the age groups < 50, 50-59, 60-69, 70-79 and ≥ 80 years. The analysis showed homogeneity in all age groups, i.e. there was the same statistically significant difference in mortality between the NDR+&Reg- and the NDR-&Reg+ population among women and men in all age groups as well as the same distribution of CHI in the age groups. A comparison of the total five-year mortality rate for the two populations was therefore meaningful, as age was not a confounder in the analysis.

Ethical approval

The study was approved by the Danish Data Protection Agency (2006-53-1385 j. no. and j. no. 2008-58-0035) and by the Regional Science Ethics Committee for Southern Denmark (j. no. S-20080097).

Trial registration: not relevant.

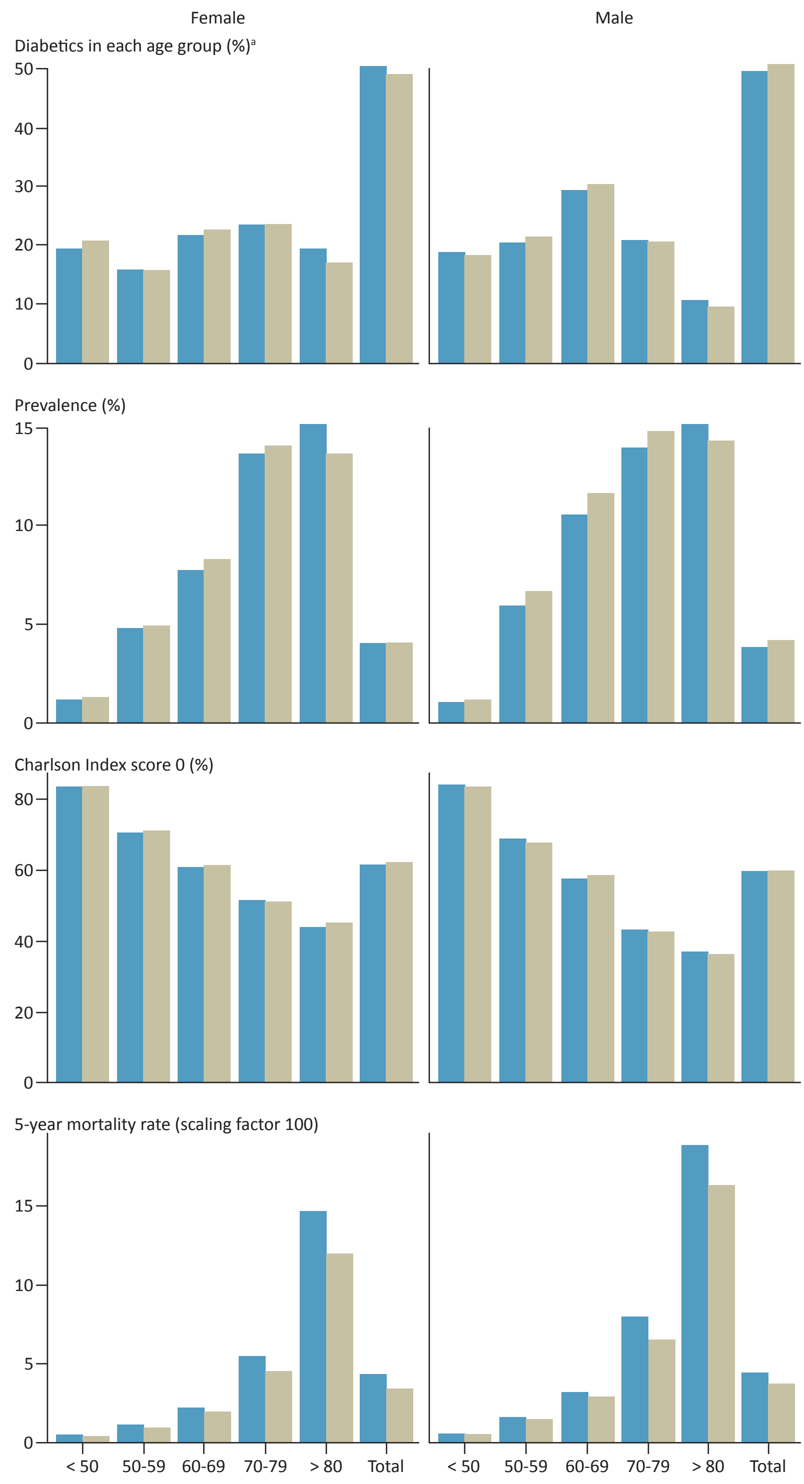
RESULTS

The number of patients

A total of 14,998 (including 47 (0.3%) self-enrolled) candidate diabetes patients residing in the former County of

FIGURE 1

Age distribution, prevalence, morbidity and five-year mortality in females and males grouped by age and totals found in the diabetes population as identified by the regional population (■) and the National Danish Diabetes Register population algorithm (■), respectively. Includes candidate diabetics residing in municipalities codes 607, 615, 630 and 766 as of 31 December 2006.



a) The bars show the percentage of women or men in age groups from < 50 to ≥ 80 yrs and they were calculated in relation to all women or men, but totals were calculated relative to the total number of women and men in the regional and national population, respectively.

TABLE 2

Outcome in clinical dimension in candidate diabetes patients identified by the national algorithm without being identified in the regional population and candidate diabetes patients identified by the regional algorithm without being identified in the National Danish Diabetes Register population as well as those identified by both algorithms. Included: diabetics residing in new municipalities 607, 615, 630 and 766 as of 31 December 2006.

		NDR+& Reg-(N = 2,279)				NDR-& Reg+ (N = 2,802[a])			
	p-value		CIS = 0	CIS: 1-2	CIS ≥ 3		CIS = 0	CIS: 1-2	CIS ≥ 3
Prevalence, %	< 0.0001[b]	0.82	–	–	–	1.01	–	–	–
Age distribution, n (%)	< 0.0001[b]								
< 50 yrs		473 (20.8)	–	–	–	614 (21.9)	–	–	–
50-59 yrs		370 (16.2)	–	–	–	510 (18.2)	–	–	–
60-69 yrs		447 (19.6)	–	–	–	707 (25.2)	–	–	–
70-79 yrs		488 (21.4)	–	–	–	606 (21.6)	–	–	–
≥ 80 yrs		501 (22.0)	–	–	–	365 (13.0)	–	–	–
< 80 yrs		1,778 (78.0)	–	–	–	2,437 (87.0)	–	–	–
	< 0.0001[c]								
≥ 80 yrs		501 (22.0)				365 (13.0)			
Charlson Index score, n (%)	< 0.05[b]								
0		1,310 (57.5)	–	–	–	1,682 (60.4)	–	–	–
1-2		752 (33.0)	–	–	–	876 (31.4)	–	–	–
≥ 3		217 (9.5)	–	–	–	229 (8.2)	–	–	–
Age group, n (%)									
< 50 yrs		–	393 (30)	73 (10)	7 (3)	–	505 (30)	94 (11)	15 (7)
50-59 yrs		–	257 (20)	95 (13)	18 (8)	–	349 (21)	137 (16)	22 (10)
60-69 yrs		–	238 (18)	161 (21)	48 (22)	–	411 (24)	235 (27)	52 (23)
70-79 yrs		–	217 (17)	200 (27)	71 (33)	–	268 (16)	250 (29)	85 (37)
≥ 80 yrs		–	205 (16)	223 (30)	73 (34)	–	149 (9)	160 (18)	55 (24)
Mantel-Haenszels OR_{total} (95% $CI_{lower-upper}$) for NDR+&Reg- versus NDR-&Reg+[d]									
CIS: 1-2	0.64	1.03 (0.91-1.17)	–	–	–	1.03 (0.91-1.17)	–	–	–
CIS ≥ 3	0.37	1.10 (0.89-1.35)				1.10 (0.89-1.35)	–	–	–
CIS ≥ 1	0.48	1.04 (0.93-1.18)	–			1.04 (0.93-1.18)	–	–	–
5-year mortality rate × 100 (95% $CI_{lower-upper}$)									
< 80 yrs		3.44 (3.03-3.84)	–	–	–	1.66 (1.43-1.90)	–	–	–
	< 0.0001[c]								
≥ 80 yrs		19.63 (17.43-21.82)	–	–	–	9.94 (8.35-11.52)	–	–	–
Overall	< 0.0001[b]	6.08 (5.59-6.58)	–	–	–	2.61 (2.33-2.88)	–	–	–

CI = confidence interval; NDR+&Reg- = identified in national algorithm but not in regional algorithm; NDR-&Reg+ = not identified in national algorithm, but in regional algorithm; NDR+&Reg+ = identified in national algorithm and in regional algorithm; OR = odds ratio.
a) A total of 15 persons were without Charlson Index information; b) For χ^2-test performed between NDR+&Reg-, NDR-&Reg+ and NDR+&Reg+; c) For χ^2-test performed between NDR+&Reg- and NDR-&Reg+; d) CIS = 0 was reference category.

TABLE 2, CONTINUES

Vejle area as of 31 December 2006 were identified via the regional algorithm. From the entire diabetes population, 11,499 diabetics resided in the municipalities 607, 615, 630, and 766 (the total population in the four municipalities was 277,273 inhabitants) within the former County of Vejle.

The total number of candidate diabetics registered in the NDR as a total for Denmark as of 31 December 2006 was 227,621 (total Danish population approximately 5.5 million) of whom 10,976 were residing in the same four municipalities.

Prevalence of diabetes in the study population

The prevalence of diabetes in the four municipalities according to the regional algorithm was 4.1, and the prevalence for diabetes patients registered in the NDR in the same geographic area was 4.0% as of 31 December 2006.

Characteristics and comparison of the regional population with the National Danish Diabetes Register

Table 1 shows the number of the candidate diabetes patients found by the components of the regional versus the national algorithm, and the characteristics of patients of both populations are presented in **Figure 1**.

There was a higher proportion (22%) of elderly ≥ 80 years in NDR+&Reg- versus NDR-&Reg+ (13%). When adjusted for age, the odds ratio (OR) for the group of individuals with a CHI score ≥ 1 compared with 0 score for NDR+&Reg- versus NDR-&Reg+ was 1.04 (p = 0.48)

TABLE 2, CONTINUED

NDR+& Reg+ (N = 8,697)			
	CIS = 0	CIS: 1-2	CIS ≥ 3
3.14	–	–	-
1,625 (18.7)	–	–	–
1,620 (18.6)	–	–	–
2,352 (27.0)	–	–	–
1,941 (22.3)	–	–	–
1,159 (13.3)			
–	–	–	–
–	–	–	–
5,313 (61.0)	–	–	–
2,633 (30.3)	–	–	–
751 (8.7)	–	–	–
–	1,362 (26)	222 (8)	41 (5)
–	1,124 (21)	414 (16)	82 (11)
–	1,410 (27)	751 (29)	191 (25)
–	933 (18)	752 (29)	256 (34)
–	484 (9)	494 (19)	181 (24)
–	–	–	–
–	–	–	–
–	–	–	–
–	–	–	–
–	–	–	–
4.05 (3.86-4.25)	–	–	–

(**Table 2**), i.e. both populations had a comparable degree of co-morbidity. In contrast, the overall age-adjusted five-year mortality rate was 6.1 per 100 patient years in the NDR+&Reg- population compared with 2.6 per 100 patient-years in the NDR-&Reg+ population (Table 2).

Ascertainment characteristics

Table 3 provides further details of ascertainment sources in the three populations NDR+&Reg-, NDR-&Reg+ and NDR+&Reg+. Of the 2,279 patients of the NDR+&Reg- population, 1,702 (75%) were exclusively identified by means of the frequency of blood glucose measurement, whereas 459 (20%) were ascertained by means of registrations in the DNPrR and/or the LPR; i.e. criteria judged to be diabetes-specific and potentially identifiable in Reg+. Of the 2,802 patients of the NDR-&Reg+ population, 1,684 (60%) were identified exclusively by means of the frequency of HbA_{1c} measurement, whereas the rest (40%) were identified by means of criteria judged to be diabetes-specific.

A total of 21% of all patients in the NDR population were identified exclusively by means of the frequency of blood glucose measurements. Conversely, in the regional population, 18% of all patients were identified exclusively by the frequency of HbA_{1c} measurement (Table 3).

The new diagnostic analysis for diabetes.

DISCUSSION

In this study, we compared the performance of two competing algorithms aiming at identifying patients with diabetes from centralised registration sources. Both the regional algorithm used in the former County of Vejle and the algorithm used in the NDR rely upon sources judged to be specific for diabetes, i.e. the registration of diabetes diagnoses in the hospital patient registration systems as well as the identification of prescriptions containing anti-diabetic drugs. In the NDR, registration of the provision of chiropody services specifically for patients with diabetes represents an additional unique ascertainment source. On the other hand, the regional algorithm makes use of the registration of HbA_{1c} measurements and the results of these measurements. Both algorithms use different ascertainment sources that may not be specific for diabetes, i.e. criteria related to the frequency of blood glucose measurements in the NDR against the frequency of HbA_{1c} measurements in the former County of Vejle.

TABLE 3

Specification of ascertainment by sources in the national algorithm and the regional algorithm, respectively. Included: diabetics residing in new municipalities: 607, 615, 630 and 766 as of 31 December 2006 (Ntotal = 13,778). The values are n.

	NDR+& Reg- (N = 2,279)	NDR-& Reg+ (N = 2,802)	NDR+& Reg+ (N = 8,697)
Ascertained in Reg by			
HbA_{1c} ≥ 6.6% exclusively	–	381	79[c]
HbA_{1c} measurement frequency[a] exclusively	–	1,684	416[d]
HbA_{1c} ≥ 6.6% *and* HbA_{1c} measurement frequency exclusively	–	303	375[e]
All other combinations of sources	2,279	434	7,827[f]
Ascertained in NDR by			
Blood glucose measurement frequency[b] exclusively	1,702	–	578[g]
Chiropody for diabetes exclusively	107	–	36[h]
Blood glucose measurement frequency *and* chiropody for diabetes exclusively	11	–	81[i]
All other combinations	459	2,802	8,002[j]

HbA_{1c} = haemaglobin A_{1c} concentration; NDR = National Danish Diabetes Register population/algorithm; NDR+&Reg- = identified in national algorithm but not in regional algorithm;
NDR-&Reg+ = not identified in national algorithm, but in regional algorithm; NDR+&Reg+ = identified in national algorithm and in regional algorithm; Reg = regional population/algorithm.
a) Criteria for HbA_{1c}: ≥ 3 HbA_{1c} measurements from January 2002 through December 2006.
b) Criteria for blood glucose measurement frequency: ≥ 2 measurements annually over 5 consecutive years and/or at least 5 measurements within a period of 1 yr.
c) Of the 79 cases, 48 were ascertained in NDR exclusively by blood glucose measurement frequency and 31 by other source(s).
d) Of the 416 cases, 332 were ascertained in NDR exclusively by blood glucose measurement frequency and 84 by other source(s).
e) Of the 375 cases, 182 were ascertained in NDR exclusively by blood glucose measurement frequency and 193 by other source(s).
f) Of the 7,827 cases, 16 were ascertained in NDR exclusively by blood glucose measurement frequency and 7,811 by other source(s).
g) Of the 578 cases, 332 were ascertained in Reg exclusively by HbA_{1c} measurement frequency and 246 by other source(s).
h) Of the 36 cases, 17 were ascertained in Reg exclusively by HbA_{1c} measurement frequency and 19 by other source(s).
Ii Of the 81 cases, 22 were ascertained in Reg exclusively by HbA_{1c} measurement frequency and 59 by other source(s).
j) Of the 8,002 cases, 45 were ascertained in Reg exclusively by HbA_{1c}c measurement frequency and 7,957 by other source(s).

The two contrasting algorithms yield similar estimates of the prevalence of diabetes. Even so, we observed a substantially higher proportion of persons above 80 years of age in the NDR, and a five-year age-adjusted mortality rate that was more than twice as high in the NDR+&Reg- as in the NDR-&Reg+ population. On the other hand, we detected no major differences in comorbidity between these two populations. Our findings suggest that the two algorithms identify two populations that have some 63% of the patients in common.

The national algorithm ascertains 21% of the registrants exclusively by means of the criteria related to frequency of blood glucose measurements; although some of these persons were identified by diabetes-specific ascertainment sources in the regional algorithm, most of them may not have diabetes. The higher mortality in the NDR+&Reg- population may at least partly be due to inclusion of subjects without diabetes, but who are frequently monitored by blood glucose measurements due to other severe diseases. Such monitoring could also be associated with poor socioeconomic and lifestyle factors, e.g. alcohol abuse and/or malnutrition associated with a poorer overall health profile in the group of NDR+&Reg- which will contribute to the significantly higher mortality. We recommend that this group of NDR+&Reg- be further explored with a view to explain the reason for their high mortality.

In the regional algorithm, 18% were ascertained exclusively by means of the frequency of HbA_{1c} measurements. Most of these persons may not have diabetes.

Since 2012, the diagnostic discrimination value for diabetes is HbA_{1c} ≥ 6.5% in Denmark [10, 11]. However, we used 6.6% as the 99.9 percentile of upper reference limits for HbA_{1c} in healthy persons [12] in our algorithm, which was developed in 2006 before the official recommendations came into force. 24% of the NDR-&Reg+ individuals were identified by at least one HbA_{1c} ≥ 6.6% without other criteria judged to be diabetes-specific (LPR and/or DNPrR). Additionally, 16% of the NDR-&Reg+ individuals were identified by diabetes-specific criteria. The remaining 60% (identified exclusively by the frequency of HbA_{1c} measurements) may not have diabetes. However, the proportion would likely be lower if the diagnostic limit of 6.5% had been used. On the other hand, 75% of the NDR+&Reg- individuals identified exclusively by the frequency of blood glucose measurements may not have diabetes.

CONCLUSION

If the criteria "at least two glucose measurements annually over five consecutive years" or "at least five glucose measurements within a period of one year" were no longer used in the national algorithm, about 21% of the registered patients would be eliminated from the NDR, but a comparable proportion of diabetics would be added based on the abnormal HbA_{1c} value criterion. If the NDR included abnormal HbA_{1c} value, the mortality rate would be reduced from approx. 4.5 to 3.7 (Figure 1). The criterion of abnormal HbA_{1c} value is the more correct way to identify patients with diabetes because an elevated HbA_{1c} is diagnostic for diabetes [10, 11]).

All measurements for HbA_{1c} are collected by the Danish Health Data Network of Medcom, and HbA_{1c} values will expectedly become searchable in the Danish Laboratory Data Bank [13].

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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk.

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