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Health-related quality of life for normal glycaemia, prediabetes and type 2 diabetes mellitus: Cross-sectional analysis of the ADDITION-PRO study

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Abstract

Aims: We estimated and compared health-related quality of life for individuals with normal glucose tolerance, prediabetes and diabetes.

Methods: Participants in the ADDITION-PRO study, Denmark, who attended a health assessment between 2009 and 2011, and who completed the 3-level EuroQoL 5-dimensions (EQ-5D-3L) questionnaire were included. For the present study, they were classified as normal glucose tolerance, prediabetes and diabetes (screen-detected and known) using the 2019 American Diabetes Association criteria. Prediabetes was defined as impaired fasting glucose, impaired glucose tolerance or HbA1c between 5.7–6.4% (39–47 mmol/mol). EQ-5D-3L data were converted into utility scores using Danish and UK values, where '1' equals full health and '0' equals death. Regression models estimated the association between utility and the different glucose health states.

Results: The mean EQ-5D-3L score in the sample population was 0.86 ± 0.17 (median 0.85, interquartile range 0.76 to 1) using UK values. Almost half of the sample (48%) reported full health with an EQ-5D score of '1'. Individuals with known diabetes reported the lowest EQ-5D-3L utility scores (0.81 ± 0.20), followed by individuals with screen-detected diabetes (0.85 ± 0.19), prediabetes (0.86 ± 0.17) and normal glucose tolerance (0.90 ± 0.15). The differences were statistically significant for normal glucose and known diabetes relative to prediabetes, after adjusting for sex, age, smoking, BMI and physical activity. These findings also held using Danish values albeit the differences were of smaller magnitude.

Conclusions: Having prediabetes and diabetes was significantly associated with lower health-related quality of life relative to normal glucose tolerance. Our estimates will be useful to inform the value of interventions to prevent diabetes or prediabetes.

KEYWORDS

EQ-5D utility, health-related quality of life; prediabetes

1 | INTRODUCTION

The global prevalence of diabetes in adults between 20 to 79 years is projected to rise from 425 million in 2017 to 629 million by 2045, currently accounting for approximately 5 million deaths and imposing significant costs on healthcare systems.[1] Elevated glycaemic levels have been shown to increase the risk of microvascular and macrovascular complications in individuals with type 2 diabetes (T2D).[2]

Individuals with early stages of glucose dysregulation, often referred to as prediabetes, are at an increased risk of developing T2D and cardiovascular disease.[3] Evidence from randomised controlled trials suggests that lifestyle interventions and oral anti-diabetic drugs can effectively delay or prevent the progression from prediabetes to diabetes.[4-7] Life style interventions could also improve health-related quality of life in populations with prediabetes.[8] However, policy decisions around lifestyle changes in prediabetes populations would need to consider not only effectiveness but also the cost-effectiveness of those interventions to assess costs and outcomes over a lifetime period.[9,10] The preferred outcome measure in economic evaluations is the quality-adjusted life year (QALY) which is obtained by multiplying the quality weight of a health state by the time spent in that state. The weights can be determined using generic quality-of-life instruments such as the 3-level EuroQol 5-dimensions (EQ-5D-3L).[11]

The aim of this study was to compare the health-related quality of life, measured with the EQ-5D-3L instrument, in individuals with normal glucose tolerance (NGT), prediabetes or type 2 diabetes. Previous studies estimating health-related quality of life across glucose states did not have HbA1c data.[12-15] This limits considerably their application to inform contemporary economic evaluations targeting these populations. Hence, we defined mutually exclusive glucose states using the 2019 American Diabetes Association (ADA) criteria[16] that considers fasting glucose, 2-hour glucose and HbA1c measurements. We used data from the same source population, the ADDITION-PRO study, to estimate the association of glucose states with health-related quality of life.

What is already known?

- Individuals with diabetes reported lower quality of life compared to normal glucose tolerance. However, HbA1c was not used as a criterion of classification.

What this study has found?

- Prediabetes and diabetes defined using the ADA 2019 criteria were significantly associated with lower health related quality of life relative to individuals with normal glucose tolerance.

What are the implication of the study?

- This is the first study to use the ADA criteria to estimate health related quality of life for normal glucose tolerance, prediabetes and diabetes from the same source population. Our results will inform the cost-effectiveness analysis of preventative interventions for diabetes.

2 | METHODS

2.1 | Study population and definition of glucose states

We used cross-sectional data from the ADDITION-PRO study. ADDITION-PRO is nested within the Danish arm (ADDITION-Denmark) of the ADDITION-Europe study.[17] ADDITION-Denmark consisted of a stepwise screening program for diabetes carried out in Danish general practices between 2001 and 2006.[18] In 2009–2011, a subset of participants with low to high risk of diabetes at screening were invited for a detailed follow-up health examination ($n = 4188$). Those invited comprised all individuals with impaired glucose regulation at screening, individuals who developed diabetes following screening, and a random sub-sample with normal glucose tolerance (NGT). A total of 2082 (50%) of the invited attended the ADDITION-PRO health examination. The health examination included biochemical and clinical measurements, all performed by trained staff, and completion of validated questionnaires, such as the EQ-5D-3L self-reported questionnaire. Here, participants without known diabetes were given a standard 75-g oral glucose tolerance test (OGTT) after an overnight fast of ≥8 h. HbA1c was measured and blood samples were drawn at 0, 30, and 120 min for assessment of plasma glucose. See study protocol for more details.[18]

The study was approved by the ethics committee of the Central Denmark Region (reference no. 20080229) and was conducted in accordance with the Helsinki Declaration. All participants provided oral and written informed consent before participating in the study.

2.2 | Classification of NGT, prediabetes and diabetes

For the present study, participants were classified in four mutually exclusive glucose states according to the

2019 classification of the American Diabetes Association (ADA)[16]:

- Known diabetes: identified based on information from the participants' general practitioners and/or self-reports at the ADDITION-PRO examination;
- Screen-detected diabetes: defined as HbA1c equal or above 6.5% (48 mmol/mol) or FPG equal or above 7.0 mmol/l or 2-hour plasma glucose after OGTT equal or above 11.1 mmol/l;
- Prediabetes: defined as HbA1c values of 5.7–6.4% (39–47 mmol/mol), impaired fasting glucose (IFG) (fasting plasma glucose level of 5.6–6.9 mmol/l) or impaired glucose tolerance (IGT) (2-hour plasma glucose level of 7.8–11.0 mmol/l after OGTT). Furthermore, the participant did not have values of HbA1c, FPG or 2-hour OGTT corresponding to the diabetes state;
- Normal glucose tolerance (NGT): defined as values of HbA1c, FPG and 2-hour OGTT all below those corresponding to the prediabetes and diabetes states.

2.3 | Measurement of health-related quality of life

Health-related quality of life data was captured through individual responses to the EQ-5D-3L questionnaire[19] which was mailed to each individual in advance of their clinical examination visit and checked for completeness before the individual finished their visit. This questionnaire determines the self-reported health status of each individual across five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Respondents were asked to choose one of three possible levels for each domain, that is, 1, 2 or 3, that reflected their 'own health state today', representing 'no problems' (1), 'some problems'(2) and 'extreme problems' (3) respectively. The responses to the questionnaire describe the EQ-5D self-reported health state (EQ-5D profile) of the individual and there are 243 possible health states/EQ-5D profiles.[19] The description of their health state (e.g. EQ-5D profile 1–1–1–2–1) was then converted into a single summary index or utility score (e.g. 0.80) so to better inform policy making and facilitate comparisons across different individuals and diseases. The conversion of responses (health state) into utility scores requires a value set, which provides a set of weights for each level in the five domains, obtained in valuation studies specific for a given country and region.[19] We converted each response to the EQ-5D-3L questionnaire into utility scores using the value set from the UK[11] as these are often used when country specific values are not available.[20] EQ-5D-3L scores are truncated at 1 (full health), with 0 representing dead, and negative values representing states worse than death. As sensitivity analysis, we re-estimated the utility scores using the value set from Denmark.[21] The lower bound of EQ-5D utility score is −0.624 and −0.594 using Danish and UK values,[11,21] respectively, for the worst possible health state (answering extreme problems for all five domains, that is, EQ-5D profile 3–3–3–3–3).

2.4 | Statistical analysis

We excluded 33 individuals with no known diabetes and who could not be classified into a glucose group due to: (1) fasting less than 8 hours prior to the health examination, (2) having unclassifiable glycaemic status or with missing data on plasma glucose (fasting and 2-hour OGTT) or HbA1c. This resulted in 2049 individuals available for the analysis. We then included only individuals with complete EQ-5D-3L data (98.7%), which resulted in the final sample of 2023 individuals.

Differences in participant characteristics by glucose state were assessed using Chi-Square tests (for count data) and ANOVA (for continuous data). We used the Kruskal–Wallis test to determine whether there were statistically significant differences in mean EQ-5D-3L utility scores between the four mutually exclusive glucose groups (NGT, prediabetes, screen-detected diabetes, known diabetes). Dunn's test was then used to identify which groups were different using the Benjamini–Hochberg stepwise adjustment for multiple comparisons.[22]

For less severe health states, EQ-5D utility data tend to show high proportions of participants reporting full health (answering 'no problems' for all 5 domains, and hence obtaining a utility value of 1). Several statistical techniques are available to account for these ceiling effects, and the limited range of utility data. Hence, when modelling the association between EQ-5D-3L utility scores and the four glucose states (NGT, prediabetes, screen-detected diabetes and known diabetes) we considered ordinary least squares model (OLS), generalised linear models (GLMs), two part models (logistic equation for first part, GLM for second part) and truncated inflated beta regression models.[23,24] The most appropriate model was chosen based on model fit and their ability to predict utility scores within the EQ-5D range (see electronic supplementary material for full details). We further adjusted the regression models to include age (centered at 66 yr), sex, current smoker status (yes/no), BMI (centered at 27.7 kg/m^2) and physical activity energy expenditure (PAEE) (centered at 30 kJ/Kg/day). We report the Hosmer and Lemeshow and Pearson correlation tests for the final model.[23] Physical activity energy expenditure was based on combined heart rate and acceleration sensing data obtained using the Actiheart

device.[18] Missing data on explanatory variables (BMI, current smoking status and PAEE) was imputed using multiple imputation via a chained model with 25 iterations and predictive mean matching.[25] The analyses were run in Stata 15.1. The significance level for all statistical tests was 0.05.

2.5 | Sensitivity analysis

We compared EQ-5D-3L utility scores after classifying all study participants according to the World Health Organization 2006 criteria: (1) NGT, (2) intermediate hyperglycaemia (IFG [6.1 to 6.9 mmol/l], IGT, or IFG+IGT), (3) screen-detected diabetes with FPG equal or above 7.0 mmol/l or 2-hour plasma glucose after OGTT equal or above 11.1 mmol/l, and (4) known diabetes. Differences in the mean EQ-5D-3L utility scores were assessed using the non-parametric Kruskal–Wallis and Dunn's tests and confirmed with the regression models as described above. Finally, we also assessed differences between glucose states defined according to ADA 2019 criteria adjusting only for age (centered at 66 years) and sex.

3 | RESULTS

3.1 | Study population and glucose states

Of the individuals in our study, 13% were classified as NGT ($n = 267$), 61% were classified as prediabetes ($n = 1234$), 10% as screen-detected diabetes ($n = 193$) and 16% as known diabetes ($n = 329$). We report in Table 1 and Table S1 the characteristics of the sample population at the ADDITION-PRO health examination. The average age at time of the follow-up examination was 66.1 ± 6.9 yr, 46% were women and mean BMI was 27.7 ± 4.7 kg/m^2. About 18% reported to be currently smoking. The diabetes group (screen-detected and known diabetes) was characterised by a higher proportion of smokers and higher BMI values compared to the prediabetes and NGT groups (Table 1). Individuals with NGT were younger, with lower BMI and higher PAEE compared to the other three groups. We found significant differences across the four groups in terms of age (ANOVA, $p < 0.001$), sex (Chi-square, $p < 0.001$), smoking status (Chi-square, $p = 0.012$), BMI (ANOVA, $p < 0.001$) and PAEE (ANOVA, $p < 0.001$).

Table 2 reports the distribution of individuals with prediabetes by glucose criteria (FPG, 2-hour OGTT or HbA1c). The majority were IFG only ($n = 385$) and IFG with elevated HbA1c ($n = 385$). Individuals with prediabetes identified solely through high HbA1c totalled 177 (14%). Individuals with IGT amounted to 287 (23%).

TABLE 1 Descriptive statistics of the ADDITION-PRO population with complete EQ-5D data at health examination

Variable	Normal glucose tolerance		Prediabetes		Screen-detected diabetes		Known diabetes	
	n	Mean ± SD/%	*n*	Mean ± SD/%	*n*	Mean ± SD/%	*n*	Mean ± SD/%
Number of individuals	267		1,234		193		329	
Age	267	63.6 ± 7.7	1,234	66.8 ± 6.6	193	65.8 ± 6.5	329	65.5 ± 6.9
Women	267	58%	1,234	45%	193	34%	329	46%
HbA1c								
mmol/mol	267	35.0 ± 2.5	1,234	38.8 ± 3.4	193	44.3 ± 7.0	329	44.7 ± 8.0
%	267	5.4 ± 0.2	1,234	5.7 ± 0.3	193	6.2 ± 0.6	329	6.2 ± 0.7
FPG (mmol/l)	267	5.2 ± 0.3	1,234	6.0 ± 0.5	193	7.2 ± 1.0	38	6.8 ± 1.6
2-hour PG (OGTT, mmol/l)	267	5.3 ± 1.1	1,234	6.6 ± 1.7	193	10.5 ± 3.2	33	9.1 ± 3.8
BMI (kg/m^2)	267	25.1 ± 3.6	1,234	27.2 ± 4.3	193	29.7 ± 5.2	328	30.3 ± 5.1
Current smoker	267	13%	1,232	17%	192	21%	327	22%
Physical activity energy expenditure (kJ/Kg/day)	201	32.9 ± 13.9	961	30.6 ± 15.4	157	27.7 ± 14.1	267	27.9 ± 14.7

Note: Normal glucose tolerance: values of HbA1c, FPG and 2-hour plasma glucose all below those corresponding to the prediabetes and diabetes states; Prediabetes: IGT and/or IFG and/or HbA1c 5.7 to 6.4% (39–47 mmol/mol); screen-detected diabetes: those found to have at the ADDITION-PRO health examination with glucose values over the diabetes threshold (FPG, 2-hour PG or HbA1c); known diabetes: identified based on information from the participants' general practitioners and/or self-reports at the ADDITION-PRO examination.

TABLE 2 Identification of mutually exclusive glucose states for those with complete EQ-5D-3L data

Reason for diagnosis	Prediabetes[a] Number (%)
IFG only	385 (31)
IFG + HbA1c	385 (31)
HbA1c only	177 (14)
IFG + IGT + HbA1c	174 (14)
IFG + IGT	81 (6.6)
IGT + HbA1c	19 (1.5)
IGT only	13 (1.1)
Total	1,234 (100)
	Diabetes[b]
FPG only	84 (16)
2-hour PG	41 (7.9)
FPG + 2 hour PG + HbA1c	27 (5.2)
FPG + 2-hour PG	15 (2.9)
HbA1c only	14 (2.7)
FPG + HbA1c	6 (1.1)
2-hour PG + HbA1c	6 (1.1)
Known diabetes at the ADDITION-PRO examination	329 (63)
Total	522 (100)

[a]IFG (impaired fasting glucose): FPG values 5.6 mmol/l to 6.9 mmol/l; IGT (impaired glucose tolerance): 2-hour plasma glucose in 75g OGTT of 7.8 mmol/l to 11 mmol/l; HbA1c: values of 5.7 to 6.4% (39–47 mmol/mol);
[b]Diabetes: known diagnosis at health examination or HbA1c equal or above 6.5% (48 mmol/mol), or FPG equal or above 7 mmol/l or 2 hour PG: 2-hour plasma glucose in 75g OGTT equal or above 11.1 mmol/l.

Of the 193 individuals with screen-detected diabetes, 84 (44%) were identified with elevated FPG only, 41 (21%) were identified with elevated 2-hour PG only, and 14 (7.3%) were identified with elevated HbA1c only. The remaining 54 (29%) were identified with a combination of elevated glucose values (see Table 2).

Table S2 reports the number of observations for all EQ-5D dimensions by glucose state group. The majority of responses across all dimensions was recorded for no problems, with the exception of the dimension of pain/discomfort in those with known diabetes who reported a higher percentage for moderate and severe problems compared to no problems. The proportion of individuals reporting some problems with usual activities or some anxiety and depression showed an increasing trend from the normal glucose tolerance to the known diabetes group. Table S3 reports the 10 most frequent EQ-5D-3L health states/profiles by glucose state. The proportion of individuals reporting full health (i.e. 1–1–1–1–1) decreased from the normal glucose tolerance (58%) to the known diabetes group (35%). The top two most frequently reported profiles represented almost three quarters of individuals in the normal glucose and prediabetes groups (full health, 1–1–1–1–1, and some problems in the pain/discomfort domain, 1–1–1–2–1). However, in the known diabetes, five profiles accounted for three quarters of individuals.

Using the UK values, the mean EQ-5D-3L score was 0.86±0.17 and the median was 0.85 (IQR: 0.76, 1) (Table S1). Almost half of the individuals reported full health at the follow-up examination, and the average utility score among those participants who reported some problems was 0.73±0.15. Figure 1 and Table 3 reports EQ −5D utility by glucose group using UK values. Mean utility scores were the highest in the normal glucose group (0.90 ± 0.15), followed by the prediabetes group (0.86 ± 0.17), the screen-detected diabetes group (0.85 ± 0.19), and those with known diabetes (0.81 ± 0.20). Utility values derived by using the Danish value set were slightly higher than the ones calculated using the UK values, which resulted in a mean score of 0.88±0.14 and a median of 0.82 (IQR: 0.78, 1) (see Figure S1; Tables S1 and S4).

3.2 | Utility differences relative to prediabetes group

The best fitting model was the two-part model (logit and OLS) (see Table S5 for model fit comparison). Table 4 shows the marginal effects of the model with UK and Danish values. We chose prediabetes as the reference glucose state due to having the largest sample size. We report in Table S6 the model coefficients. The models passed the H-L and Pearson tests.

Using UK values, individuals with normal glucose tolerance were associated with significantly higher utility (0.024, 95%CI: 0.002 to 0.046) relative to those with prediabetes, adjusting for age, sex, BMI, smoking status and PAEE. The difference in utility between individuals with prediabetes and screen-detected diabetes was not statistically significant. Individuals with known diabetes were associated with a significant lower utility relative to prediabetes (−0.036, 95%CI: −0.058 to −0.014). These findings also held using Danish values (see Table 4) albeit the differences were of smaller magnitude (e.g. −0.031 vs. −0.036 for known diabetes relative to prediabetes).

3.3 | Sensitivity analysis

Using the classification criteria from the World Health Organization 2006, 44% were now classified as NGT (n = 887), followed by 31% as having prediabetes (n = 628), 16% with known T2D (n = 329), and 9% with screen-detected T2D (n = 179) (see Table S7). Hence, the

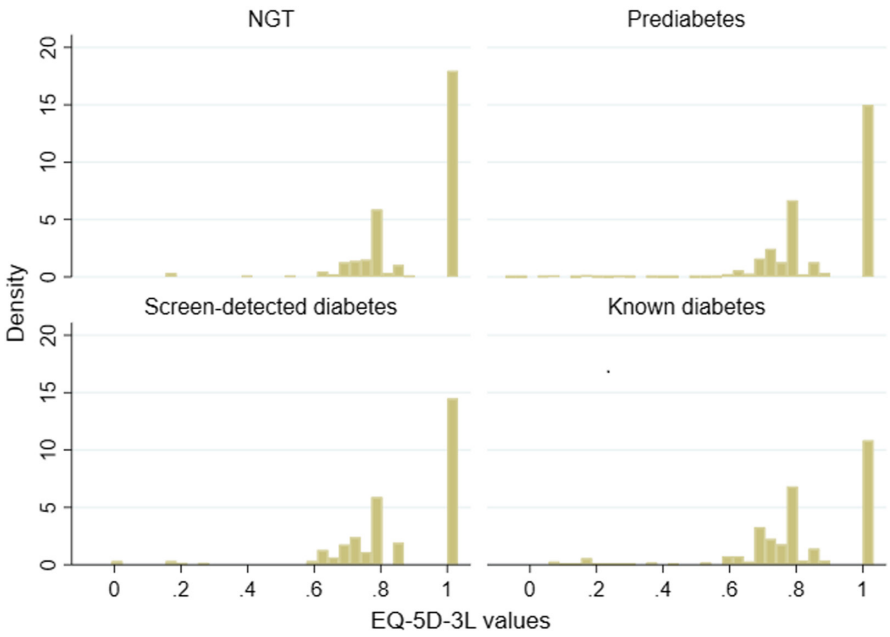

FIGURE 1 Distribution of EQ-5D-3L values using the UK value set by glucose state*.
*EQ-5D-3L score of 1 equals full health and 0 equals death. To facilitate comparisons between states we are reporting density units in y-axis so that the area under each histogram is equal to 1

largest shift was the reclassification of significant numbers of individuals as normal glucose tolerance from the prediabetes group using the ADA criteria. Using UK values, individuals with known diabetes were associated with significant lower utility relative to prediabetes (−0.039, 95%CI: −0.062 to −0.016) (see Table S8). However, there were no significant differences in EQ-5D-3L score between prediabetes and NGT or screen-detected diabetes groups. These findings also held using Danish values (see Table S8).

Using UK values and ADA 2019 criteria and adjusting only for sex and age, individuals with normal glucose tolerance and known diabetes were associated with significantly higher utility (0.037, 95%CI: 0.016 to 0.059) and lower utility (−0.054, 95%CI: −0.075 to −0.033), respectively, relative to those with prediabetes (see Table S9). Hence, the differences were of higher magnitude compared to those estimated after further adjusting for BMI, smoking status and physical activity (see Table 4).

4 | DISCUSSION

This cross-sectional study highlights that individuals with prediabetes and known diabetes reported significantly lower health-related quality of life compared to those with normal glucose tolerance. The group with known diabetes reported the highest percentage of moderate and severe problems in the 'pain/discomfort' dimension of all glucose groups. There was also an increasing trend in those reporting problems in the usual activities and anxiety/depression dimensions from NGT to known diabetes.

To the best of our knowledge, this is the first study to use HbA1c and the ADA 2019 criteria to produce EQ-5D utility scores for normal glucose, prediabetes and diabetes from the same source population. Previous studies have reported health utilities for these glucose states in Dutch, Swedish, Finnish and Greek populations using instruments such as SF-36,[12] HRQOL-15D[14,15] and the EQ-5D-3L.[13] However, these studies did not use HbA1c as a criterion of classification but rather the WHO 1999 criteria[12-14] or the ADA criteria without the HbA1c information.[15] This is a significant limitation to their application to inform contemporary economic evaluations targeting these populations. Consistent across all studies and health-related quality of life instruments was that individuals with diabetes reported the lowest utility scores and there was a decreasing trend in scores from normal glucose to diabetes. This is aligned with the findings from our study using either the ADA or the WHO criteria. The Dutch study used the EQ-5D-3L instrument and reported similar utility values for diabetes as our study (0.86 vs. 0.85 in this study using Danish tariffs).[13] Comparisons with the other three studies are more challenging due to the use of different instruments. Overall, only one study reported a significant difference in utility scores between the normal glucose and prediabetes groups, the remaining three did not. This is consistent with our findings when we applied the WHO criteria as a sensitivity analysis.[13] The exception was the Finnish study that reported the odds of reporting lower health-related quality of life to be significant with IGT compared to normal glucose.[14] However, this was not replicated in our study using the WHO criteria for classification. Finally, in addition to other studies, we

TABLE 3 EQ-5D scores per glucose state group at health examination (UK value set)

	Normal glucose tolerance			Prediabetes			Screen-detected diabetes			Known diabetes		
Variable	**Number (%)**	**Mean ± SD**	**Median (IQR)**	**Number (%)**	**Mean ± SD**	**Median (IQR)**	**Number (%)**	**Mean ± SD**	**Median (IQR)**	**Number (%)**	**Mean ± SD**	**Median (IQR)**
EQ-5D utility score	267 (99)	0.90 ± 0.15	1 (0.80,1)	1234 (99)	0.86 ± 0.17	0.85 (0.80, 1)	193 (98)	0.85 ± 0.19	0.85 (0.76,1)	329 (97)	0.81 ± 0.20	0.80 (0.73, 1)
Reporting full health (score = 1)	156 (58)			602 (49)			91 (47)			118 (35)		
EQ-5D utility score for those reporting problems	111 (42)	0.75 ± 0.12	0.80 (0.73, 0.80)	632 (51)	0.74 ± 0.14	0.80 (0.73, 0.80)	102 (53)	0.72 ± 0.16	0.76 (0.69,0.80)	213 (65)	0.70 ± 0.17	0.76 (0.69, 0.80)

Note: Normal glucose tolerance: values of HbA1c, FPG and 2-hour plasma glucose all below those corresponding to the prediabetes and diabetes states; Prediabetes: IGT and/or IFG and/or HbA1c 5.7 to 6.4% (39–47 mmol/mol); screen-detected diabetes: not known as having diabetes prior to ADDITION-PRO examination and with glucose values within diabetes threshold (FPG, 2-hour PG or HbA1c); known diabetes: identified based on information from the participants' general practitioners and/or self-reports at the ADDITION-PRO examination.

adjusted for potential confounding by BMI and PAEE, and the differences in EQ-5D utility scores remained significant for NGT and diabetes relative to prediabetes.

We found similar utility scores between prediabetes and screen-detected individuals and, hence, untreated type 2 diabetes. Individuals with screen-detected diabetes were not aware of their condition when completing the EQ-5D-3L. The similarity in utility scores may potentially reflect the lack of a diabetes diagnosis. Furthermore, it may reflect the early disease stage amongst screened-detected, as diabetes-related complications are major drivers of changes in health-related quality of life[26] and are likely to occur later in diabetes progression.

We believe our study demonstrates the usefulness, in research contexts, of HbA1c in combination with FPG and 2-hour glucose to distinguish participants in terms of their self-reported health-related quality of life. For example, it allowed us to identify a significant difference in health-related quality of life between the NGT and prediabetes groups. The difference between the NGT and prediabetes groups may indicate an opportunity for clinicians to address quality of life at an earlier stage of disease progression, i.e. before diabetes develops. Also, previous work has shown EQ-5D-3L scores to provide potentially valuable clinical information on the risk of mortality and complications above clinical history and established risk factors alone.[27] Our results add to previous findings showing that diagnosis of prediabetes or T2D based on fasting glucose, 2-hour glucose, or HbA1c identified people with a different underlying pathophysiology.[28] The differences in self-reported health-related quality of life data reported in this study provides further evidence of heterogeneity across groups. However, it remains unclear whether the differences in health-related quality of life are due to differences in pathophysiology. Further research is warranted into the association between insulin resistance and beta cell function and health-related quality of life.

A main strength of this study was the large number of individuals included in the analyses and the very low levels of missing data concerning the EQ-5D-3L questionnaire and glucose measurements. A limitation is the lack of EQ-5D-3L data during the step-wise screening for ADDITION-DK. This resulted in a cross-sectional analysis of health-related quality of life data from ADDITION-PRO participants and did not allow us to mitigate the potential bias arising from not adjusting for patient specific time-invariant characteristics.[26] Also, the cross-sectional nature of the study is vulnerable to potential misclassification of individuals given the intra-individual variation in fasting, 2-hour plasma glucose and HbA1c levels.[29,30] Another potential limitation was the high percentage of

TABLE 4 Marginal effects (ME) of glucose states on EQ-5D-3L scores

Dependent variable	EQ-5D-3L with UK values	EQ-5D-3L with Danish values
Type of model	2-part model (logit and OLS)	2-part model (logit and OLS)
Sample size	2023	2023
Variables	ME (95%CI)	ME (95%CI)
NGT vs. prediabetes	0.024 (0.002, 0.046)	0.020 (0.002, 0.038)
Screen-detected diabetes vs. prediabetes	−0.006 (−0.033, 0.020)	−0.007 (−0.028, 0.014)
Known diabetes vs. prediabetes	−0.036 (−0.058, −0.014)	−0.031 (−0.049, −0.014)
Adjusted for age, sex, smoking status, BMI and PAEE		
Hosmer-Lemeshow *p*-value	0.760	0.944
Pearson correlation *p*-value	0.783	0.799

Note: Marginal effects measure the association with EQ-5D-3L score changes when the glucose state changes, holding all other variables constant (age, sex, smoking status, BMI and PAEE). For example, a change from NGT to prediabetes is associated with an increase in EQ-5D-3L score of 0.024 in the UK model, holding all else constant.

individuals (61%) that were classified as having prediabetes during the ADDITION-PRO health examination. This limited the power to obtain more precise estimates of utility differences across the glucose groups. Furthermore, we did not have access to data on medications and clinician-confirmed comorbidities to allow adjustments for these. Finally, HbA1c was not used to base the sampling of participants for the ADDITION-PRO study at a step-wise screening 5–7 yr before the ADDITION-PRO health examination.[18] Sampling was mainly based on 2-hour plasma glucose levels, which meant that there was a larger chance of being classified with prediabetes or screen-detected diabetes based on 2-hour plasma glucose result than by HbA1c. Therefore, the distribution of participants according to the different diagnostic criteria may not be representative of general Danish population. However, the differences in utility scores found between groups should still apply to the general population in Denmark and potentially to other populations.

Our results show that having prediabetes and diabetes was significantly associated with lower health-related quality of life relative to individuals with normal glucose tolerance. This seems to be due to individuals in the latter group experiencing more difficulties in the dimensions of pain/discomfort, usual activities and anxiety/depression. Our estimates will be useful to inform the effectiveness and cost-effectiveness analysis of preventive interventions for diabetes.

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AUTHOR CONTRIBUTIONS

J.L. analysed the data and drafted the manuscript. F.B. analysed data. J.L., E.P. and T.F. conceived the idea, designed the study, provided input on statistical analysis and participated in the drafting of the manuscript. J.L., F.B., D.V., T.M.J and M.E.J. provided input on statistical analysis and interpretation of results. All authors reviewed and edited the manuscript and accepted the final version for publication. J.L. had the final responsibility for the decision to submit for publication. J.L. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICT OF INTEREST

No potential conflicts of interest were reported.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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