

Progression rates from HbA_{1c} 6.0-6.4% and other prediabetes definitions to type 2 diabetes: A meta-analysis.

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Abstract

Aims/hypothesis. Precise estimates of progression rates from “prediabetes” to type 2 diabetes are needed to optimise prevention strategies for high-risk individuals. There is acceptance of prediabetes defined by impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), but some controversy surrounding HbA_{1c}-defined prediabetes ranges, with some favouring 6.0-6.4% (42-46mmol/mol). Comparing progression rates between groups might aid this issue, thus we aimed to accurately estimate progression rates to diabetes from different prediabetes categories.

Methods. Meta-analysis of prospective observational studies where participants had prediabetes at baseline (ADA-defined IFG [5.6-6.9mmol/l], WHO-defined IFG [6.1-6.9mmol/l], IGT (7.8-11.0mmol/l) or raised HbA_{1c} [6.0-6.4%/42-46mmol/mol]) and were followed-up for incident diabetes. Incidence rates were combined using Bayesian random effects models.

Results. Overall, 70 studies met the inclusion criteria. In the six studies that used raised HbA_{1c}, the pooled incidence rate [95% Credible Interval] of diabetes was 35.6 [15.1, 83.0] per 1000 person-years. This rate was most similar to that for ADA-defined IFG (11 studies; 35.5 [26.6, 48.0]) and was non-significantly lower than WHO-defined IFG (34 studies; 47.4 [37.4, 59.8]), IGT (46 studies, 45.5 [37.8, 54.5]) and IFG plus IGT (15 studies, 70.4 [53.8, 89.7]). Similar results were seen when analysing the data by the criteria used to diagnose diabetes.

Conclusions/interpretation. This study provides evidence that progression rates differ by prediabetes definition, which has implications for the planning and implementation of diabetes prevention programmes. HbA_{1c} 6.0-6.4% might identify people at a lower diabetes risk than other prediabetes definitions, but further research is needed.

Keywords. Diabetes Mellitus, Type 2; Disease Progression; Hemoglobin A1c Protein, Human; Prediabetic State.

Abbreviations. ADA, American Diabetes Association; FBG, Fasting Blood Glucose; IFG, Impaired Fasting Glucose; IGT, Impaired Glucose Tolerance; WHO, World Health Organization.

Introduction

Type 2 diabetes has adverse outcomes including early mortality [1], and is traditionally defined by the World Health Organization (WHO) based on oral glucose tolerance tests (OGTTs) as fasting blood glucose (FBG) $\geq 7.0\text{mmol/l}$ or two-hour glucose $\geq 11.1\text{mmol/l}$ (glucose taken two hours after consuming a standard 75g glucose dose) [2]. Blood glucose is, however, continuous and evidence suggests that people with high, but not diabetes range, glucose levels still risk developing diabetes complications and have a high risk of developing overt diabetes. Therefore, this condition is often referred to as ‘prediabetes’. Controversy surrounds this terminology and the use of hyperglycaemia cut-points, but identifying high risk groups is useful for planning and implementing diabetes prevention programmes.

Different prediabetes definitions exist; mostly based on FBG (impaired fasting glucose, IFG) or two-hour glucose (impaired glucose tolerance, IGT). The WHO 1999 criteria define prediabetes as FBG between 6.1-6.9mmol/l (IFG_{WHO}) and/or two-hour glucose between 7.8-11.0mmol/l [2]. The American Diabetes Association (ADA) 2003 criteria define prediabetes as FBG between 5.6-6.9mmol/l (IFG_{ADA}) [3]. There is recent interest in prediabetes defined using glycosylated haemoglobin (HbA_{1c}). In 2011, the WHO added HbA_{1c} $\geq 6.5\%$ (48mmol/mol) to their diabetes definition, but concluded that there was insufficient evidence regarding an HbA_{1c} prediabetes range [4]. Conversely, ADA have added HbA_{1c} between 5.7-6.4% (39-46mmol/mol) to their prediabetes definition [5], while the International Expert Committee [6] and the UK-based National Institute for Health and Clinical Excellence [7] support using 6.0-6.4% (42-46mmol/mol).

We conducted a meta-analysis of progression rates from different prediabetes definitions to diabetes in observational studies. Our aim was to provide accurate estimates of progression rates focussing on whether HbA_{1c} between 6.0-6.4% (HbA_{1c6.0-6.4%}) had a similar progression rate to other accepted definitions to address the gap in knowledge regarding this definition.

Research Design and Methods

Data sources

We searched Ovid Medline (from 1993 to 10th February 2012) and Embase (from 1993 to Week 5 2012) using a search strategy constructed with a clinical librarian (ESM Appendix 1). It used Medical Subject Headings and free text terms covering “prediabetes”, “type 2 diabetes”, and “progression”, restricted to articles written in English and pertaining to humans. Reference lists of relevant systematic reviews and articles were hand searched. We then removed duplicate publications and reviewed the articles to identify studies that met the inclusion criteria. These criteria were: 1)

observational prospective study, 2) at least a subset of the participants had IFG_{ADA}, IFG_{WHO}, IGT, IFG+IGT or HbA_{1c}6.0%-6.4% at baseline, 3) the prediabetes group were followed-up, 4) incident diabetes was reported, and 5) all subjects were aged ≥ 18 years at baseline. Studies were excluded if participants received bariatric surgery or any lifestyle or pharmacological intervention likely to affect progression rates. Where a study was reported in multiple publications, the publication with the highest total person-years was included. Authors were contacted to obtain missing data.

Meta-analysis

The main outcome was the pooled incident rate (IR) of type 2 diabetes per 1000 person-years for each prediabetes definition. Data are presented as pooled IR (95% Credible Interval [CrI]) where a CrI is the Bayesian equivalent of a confidence interval. The IRs were estimated using Bayesian random effects meta-analysis with vague priors in WinBUGS v1.4.3, assuming that the incident cases had a Poisson distribution and the log IR was Normally distributed. Models were fitted for all studies and separately by diabetes diagnostic criteria. Heterogeneity was estimated using the between-study variance (τ^2). Sources of heterogeneity were explored using univariate meta-regression, with study-level covariates as the explanatory variables. As an example, the WinBUGS code to fit one of the models is in ESM Appendix 2. The remaining WinBUGS code is analogous and available from the authors upon request.

Results

The literature search identified 70 eligible studies (ESM Figure 1) whose characteristics are in ESM Table 1. Pooled IRs of diabetes per 1000 person-years are in Table 1. When any diabetes definition was allowed, the IR was lowest for IFG_{ADA} followed by IGT, IFG_{WHO}, and IFG+IGT. However, scrutiny of the CrIs shows that only IFG+IGT had a significantly higher IR than the other categories and IFG_{ADA}, IFG_{WHO} and IGT were not significantly different from each other. These results were fairly consistent regardless of diabetes definition.

The IR for HbA_{1c}6.0-6.4% was most similar to the IFG_{ADA} rate, though not significantly different from any of the other rates, when any diabetes definition was allowed and when the diabetes criteria included HbA_{1c}. When the diabetes criteria included FBG, the HbA_{1c}6.0-6.4% rate based on two studies was most similar to IFG_{WHO}. No studies that included HbA_{1c}6.0-6.4% used two-hour glucose to diagnose diabetes. Heterogeneity (τ^2) ranged from 0.18 to 1.10, with most of the prediabetes subgroups showing low to moderate heterogeneity (Table 1).

The IRs were unadjusted, therefore the effect of well-established diabetes risk factors on the IRs was investigated through meta-regression (Table 2). The incidence rate ratios were not significant, except in the IFG_{WHO} group, mean body mass index was inversely associated with progression, and there was a lower progression rate in Europe than Asia in the IFG_{WHO} (Asia: IR=60.6 [48.0, 76.2], Europe: IR=33.0 [15.7, 66.3]) and IFG+IGT (Asia: IR=100.8 [77.9, 126.8], Europe: IR=53.2 [25.4, 102.8]) groups.

Discussion

Accurately describing progression rates to type 2 diabetes is clinically important for accurately identifying people at particularly high risk and for effectively planning interventions and monitoring of these people. Thus, we used meta-analysis to pool existing estimates of progression rates within different prediabetes definitions.

The groups identified by IFG and IGT have relatively little overlap leading to suggestions that fasting and post-challenge hyperglycaemia are driven by different biological mechanisms [8]. It is suggested that IGT is the result of excessive endogenous glucose production (insulin action defect) in combination with beta-cell dysfunction (insulin secretion defect). Conversely, after food ingestion this mainly hepatic glucose output is appropriately suppressed in individuals with isolated IFG, suggesting an insulin secretory defect is mainly responsible for resultant plasma hyperglycaemia in this condition. Our findings regarding IRs in IFG and IGT groups are consistent with a systematic review conducted in 2007 [9], with the ADA's finding that their IFG definition had a lower specificity but a higher sensitivity than the WHO's [10], and with the knowledge that having IFG+IGT is typically associated with later phases of glucose intolerance [8].

Since HbA_{1c} was added to the diabetes criteria [4], there has been interest in prediabetes defined using HbA_{1c}, but current guidelines conflict regarding which definition to use, primarily due to insufficient data [5-7]. Some expert committees favour the range 6.0-6.4% [6, 7]. In that group, we estimated that 36 new diagnoses of diabetes would be expected per 1000 person-years. Although the wide CrIs make interpretation difficult, it appears that this measure relates most closely to the IFG_{ADA} category. Our data suggest HbA_{1c}6.0-6.4% is associated with a slightly lower diabetes risk than IFG_{WHO} and IGT and reinforces the need for further research establishing the predictive capacity of HbA_{1c}6.0-6.4%.

Within some subgroups, there was high heterogeneity, which we explored using study-level covariates. Few covariates were significant, suggesting that the heterogeneity was either due to covariates that were not considered or chance. The way in which diabetes was defined appeared to

play a role because on the whole heterogeneity was reduced when analyses were stratified by diabetes criteria. Glucose and HbA_{1c} appear to detect different diabetes populations [8]. The way in which prediabetes and diabetes were defined were closely related, which resulted in very small numbers of studies in some subgroups making comparisons difficult. However, progression rates were similar when fasting glucose or two-hour glucose was included. Too few studies used HbA_{1c} as a diabetes criterion to make useful conclusions, suggesting that this is an area where future research is required, particularly when it is considered that HbA_{1c} is now commonly being used to diagnose diabetes in clinical practice.

Our conclusions have limitations. The analysis was confined to existing prediabetes categories, did not include progression to diabetes from normoglycaemia or regression to normoglycaemia from prediabetes, and heterogeneity probably contributed to some overlap of CrIs thereby influencing outcome comparisons. Furthermore, the diabetes definition in some studies was not restricted to biochemical confirmation, but could utilise physician diagnosis or medication initiation as diabetes end-points. The validity of directly comparing populations whose primary outcome is defined by different criteria is justified here because the aim of the study was to report cumulative progression rates using established and internationally accepted criteria.

Whilst acknowledging the inherent difficulties associated with combining population-level observational datasets in meta-analyses of this kind, we feel this study has major strengths. To our knowledge, this is the largest predictive meta-analysis of IFG, IGT and raised HbA_{1c} categories. Moreover, rigorous methodology ensured literature searches and statistical analyses met accepted standards for meta-analyses.

We provided pooled estimates of progression rates from prediabetes to diabetes that suggest that rates were lowest for IFG, slightly higher for IGT and highest for IFG+IGT. HbA_{1c}6.0-6.4% had a similar diabetes risk to IFG_{ADA}. Further investigation is justified since non-significance meant that our results were not conclusive. These findings suggest that different management strategies might be required in future prevention programmes.

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Duality of interest: KK and MJD are members of the National Institute for Health and Clinical Excellence (NICE) committee and are also part of the Department of Health group recommending HbA_{1c} for the identification of high risk people. The other authors have no conflicts of interest to declare.

Contribution statement: KK, MJD and BS conceived the study. DM, FA and BS designed the literature search. DM, FA, DW and LG conducted the literature search. DM and FA extracted the data. DM performed the data analysis with contributions from LG and FA. DM and DW wrote the first draft and all authors were involved in the data interpretation, writing and revising the manuscript and approved the final version. DM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Table 1. Pooled incidence rate of diabetes per 1000 person-years according to different criteria used to diagnose prediabetes and diabetes.

Prediabetes definition	Criteria used to diagnose diabetes											
	Any			Included fasting glucose			Included post-load glucose			Included HbA _{1c}		
	N	IR (95% CrI) ^a	τ^2	N	IR (95% CrI)	τ^2	N	IR (95% CrI)	τ^2	N	IR (95% CrI)	τ^2
IFG _{ADA} ^b	11	35.54 (26.60, 48.02)	0.22	11	35.54 (26.60, 48.02)	0.22	4	33.04 (11.43, 102.10)	1.42	2	37.18 (0.22, 6399)	10.3
IFG _{WHO} ^c	34	47.40 (37.39, 59.81)	0.42	31	48.56 (39.56, 59.11)	0.26	17	41.58 (28.24, 60.88)	0.53	1	66.4	
IGT	46	45.46 (37.76, 54.52)	0.35	37	45.71 (37.68, 55.11)	0.31	39	47.39 (39.63, 56.53)	0.28	1	96.68	
IFG and IGT	15	70.36 (53.78, 89.71)	0.18	14	72.91 (55.26, 93.62)	0.18	12	74.92 (55.45, 98.43)	0.20	0		
Raised HbA _{1c} ^d	6	35.62 (15.14, 82.97)	1.10	2	56.55 (0.05, 62040)	19.28	0			4	25.63 (10.06, 77.56)	1.21

Abbreviations: ADA, American Diabetes Association; CrI, Credible Interval; IFG, Impaired Fasting Glucose; IGT, Impaired Glucose Tolerance; IR, Incidence Rate; WHO, World Health Organisation.

^a IR shows the pooled incidence rate of diabetes per 1000 person-years.

^b IFG defined as fasting glucose 5.6-6.9mmol/l. Only one study used ADA criteria for IFG and reported rates in the isolated IFG group, thus there are insufficient data for a meta-analysis.

^c IFG defined as fasting glucose 6.1-6.9mmol/l.

^d HbA_{1c} in the range 6.0-6.4% (42-46mmol/mol).

Table 2. Incidence rate ratios (95% Credible Interval) showing the effect of study level covariates on incidence rates of diabetes.

Study level covariate	Prediabetes group				
	IFG _{ADA}	IFG _{WHO}	IGT	IFG and IGT	Raised HbA _{1c} ^a
Mean age, years	1.00 (0.94, 1.06)	0.97 (0.94, 1.00)	0.99 (0.97, 1.01)	0.99 (0.95, 1.03)	0.95 (0.75, 1.21)
Year published, years	0.95 (0.82, 1.10)	1.02 (0.94, 1.09)	0.99 (0.96, 1.03)	1.04 (0.96, 1.12)	0.73 (0.32, 1.77)
Male, %	1.00 (0.98, 1.01)	1.01 (1.00, 1.02)	0.99 (0.99, 1.00)	1.01 (0.99, 1.03)	1.02 (0.99, 1.06)
White European, %	1.00 (0.96, 1.03)	1.00 (0.99, 1.00)	0.99 (0.99, 1.00)	1.00 (0.98, 1.01)	0.99 (0.92, 1.06)
Family history of diabetes, %	1.01 (0.99, 1.02)	1.00 (0.97, 1.03)	1.01 (1.00, 1.01)	0.99 (0.97, 1.01)	0.95 (0.82, 1.09)
Mean body mass index, kg/m ²	1.04 (0.93, 1.17)	0.86 (0.75, 0.99)	1.03 (0.92, 1.16)	0.95 (0.77, 1.17)	0.89 (0.46, 1.77)
<i>Continent</i>					
Asia	Reference	Reference	Reference	Reference	Reference
Europe	0.42 (0.17, 1.03)	0.57 (0.33, 0.96)	0.65 (0.41, 1.03)	0.55 (0.35, 0.84)	0.21 (0.02, 2.03)
Americas	1.04 (0.54, 2.02)	0.76 (0.36, 1.59)	1.01 (0.63, 1.61)	0.62 (0.37, 1.00)	0.30 (0.02, 4.96)
Other	No studies	0.69 (0.31, 1.55)	1.18 (0.64, 2.19)	No studies	0.59 (0.03, 9.41)

Abbreviations: IFG, Impaired Fasting Glucose; IGT, Impaired Glucose Tolerance.

^a 6.0-6.4% = 37-46mmol/mol.

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