Incidence Rates of Type 2 Diabetes in People With Impaired Fasting Glucose (ADA vs. WHO Criteria) and Impaired Glucose Tolerance: Results From an Older Population (KORA S4/F4/FF4 Study)

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The American Diabetes Association (ADA) Expert Committee introduced impaired fasting glucose (IFG: 100–125 mg/dL [5.6 to 6.9 mmol/L]) as a category with an increased risk for diabetes (1). The World Health Organization (WHO) defined a higher IFG cut point of 110 mg/dL (6.1 mmol/L) because using the lower cut point would substantially increase IFG prevalence and there was no evidence it would lead to reduced progression to diabetes (2).

Our aim was to estimate the long-term incidence of type 2 diabetes in people with isolated IFG (i-IFG), isolated impaired glucose tolerance (i-IGT), and combined IFG/IGT. Contrary to previous studies, we split IFG into two subcategories (i-IFG$_{low}$: 100 to <110 mg/dL; i-IFG$_{high}$: 110 to <126 mg/dL) according to the ADA and WHO cut points. We used oral glucose tolerance test (OGTT) data from the Cooperative Health Research in the Region of Augsburg (KORA) S4/F4/FF4 cohort study collected on 1,231 participants without known diabetes aged 55–74 years at baseline (1999–2001) and in two follow-up examinations (2006–2008 and 2013–2014) (3). Incident type 2 diabetes was defined as fasting glucose ≥126 mg/dL, 2-h glucose ≥200 mg/dL, or a type 2 diabetes diagnosis confirmed by a physician. We included 913 people (74%) with an OGTT or physician-confirmed type 2 diabetes at one or both follow-up investigations. Participants who died after baseline were either excluded if no data on their glycemic status during follow-up were available or censored if these data were available at the first follow-up examination. The mean follow-up time was 10.2 years. Self-reported age at diabetes diagnosis was used for calculation of person-years with physician-diagnosed diabetes during follow-up. Person-years was from baseline to the earliest of diagnosis of diabetes or last study date. For the binary response "incident diabetes" a log-linear model with a Poisson working likelihood and robust standard errors was fitted to estimate relative risks (RRs) with 95% CIs adjusted for age, sex, BMI, physical activity, smoking, and hypertension. To additionally account for the time until incident diabetes, we fitted an adjusted accelerated failure time (AFT) model for interval-censored data with a log-logistic distribution assumed for the event times. The expected time until incident diabetes for the prediabetes categories is e^{β} (β regression coefficient) × the expected time until diabetes for a person with normal glucose tolerance (NGT).

Table 1 shows the baseline characteristics and incidence rates of type 2 diabetes by OGTT categories. The mean age ± SD of participants at baseline was 63 ± 5 years (51% men). Compared with the NGT group, people with prediabetes were older, included larger proportions

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Table 1—Incidence rates and adjusted RRs for type 2 diabetes by glycemic status at baseline (IFG and IGT), with IFG split into two categories, i-IFG$_{low}$ (100 to <110 mg/dL) and i-IFG$_{high}$ (110 to <126 mg/dL): the KORA S4/F4/FF4 study[a]

OGTT category	*N* (%)	Age, years (% men)	BMI (kg/m^2)	Hypertension[b]	Current smokers	Physically inactive[c]	Incident diabetes, *n* (%)	Incidence rate per 1,000 py (95% CI)	RR (95 CI)[d]	Exp(β) from AFT model (95% CI)[d,e]
NGT	463 (51)	62.7 ± 5.4 (43)	27.3 ± 4.0	39.9	14.9	50.5	29 (6.3)	5.8 (3.9–8.3)	1.0	1.0
i-IFG$_{low}$ (100 to <110 mg/dL)	202 (22)	63.0 ± 5.4 (58)	28.4 ± 4.0	51.2	11.4	48.8	30 (14.9)	14.4 (9.7–20.5)	2.0 (1.2–3.3)	0.79 (0.66–0.93)
i-IFG$_{high}$ (110 to <126 mg/dL)	75 (8)	63.1 ± 4.9 (69)	29.5 ± 3.7	62.7	9.3	60.0	34 (45.3)	47.4 (32.8–66.2)	5.6 (3.6–8.8)	0.52 (0.43–0.63)
i-IGT	63 (7)	65.6 ± 5.4 (41)	29.0 ± 4.1	69.8	6.4	58.7	21 (33.3)	35.2 (21.8–53.8)	4.3 (2.6–7.2)	0.56 (0.46–0.69)
Combined i-IFG$_{low}$ (100 to <110 mg/dL) and IGT	59 (6)	64.5 ± 5.3 (58)	30.2 ± 4.3	59.3	3.4	54.2	27 (45.8)	52.2 (34.4–75.9)	5.5 (3.5–8.8)	0.46 (0.38–0.56)
Combined i-IFG$_{high}$ (110 to <126 mg/dL) and IGT	51 (6)	63.8 ± 4.8 (63)	29.4 ± 3.6	70.6	15.7	64.7	30 (58.8)	76.0 (51.3–108.5)	7.2 (4.6–11.3)	0.37 (0.30–0.46)
Total	913 (100)	63.2 ± 5.4 (51)	28.1 ± 4.1	49.3	12.4	52.5	171 (18.7)	18.3 (15.6–21.2)	—	—

Data are means ± SD or percentages, unless otherwise indicated. The i-IFG group had normal 2-h glucose; the i-IGT group had normal fasting glucose. py, person-years. [a]Overall mean follow-up was 10.2 years. Follow-up was 10.9 years for NGT, 10.4 years for i-IFG$_{low}$, 9.6 years for i-IFG$_{high}$, 9.5 years for i-IGT, 8.8 years for i-IFG$_{low}$/IGT, and 7.7 years for i-IFG$_{high}$/IGT. [b]Systolic/diastolic blood pressure ≥140/90 mmHg and/or use of antihypertensive medication if the subjects were aware of being hypertensive. [c]Less than 1 hour of leisure-time physical activity per week in summer or winter. [d]Adjusted for age, sex, BMI, hypertension, physical activity, and smoking. [e]For example, for i-IGT exp(β) 0.56 means the expected time until incident diabetes for people in the i-IGT group is the expected time until diabetes for people with NGT × 0.56.

of men (except in the i-IGT category), had higher BMI, and had a higher prevalence of hypertension. There were no consistent differences in current smoking between the prediabetes and NGT groups, whereas low physical activity was more often reported in prediabetes (except i-IFG$_{low}$).

When compared with the NGT group, the risk of type 2 diabetes was increased in all prediabetes categories. RR ranged from 2.0 (95% CI 1.2–3.3) in i-IFG$_{low}$ to 5.6 (3.6–8.8) in i-IFG$_{high}$ and 7.2 (4.6–11.3) in combined IFG$_{high}$/IGT. In the latter group, more than half of the people developed diabetes, whereas in those with i-IFG$_{low}$ only 15% progressed to diabetes. All prediabetes groups were associated with a reduced time to incident diabetes compared with NGT. The expected time until diabetes for i-IGT$_{low}$ was 79% of the expected time until diabetes for NGT, and for combined IFG$_{high}$/IGT it was 37%. i-IFG$_{high}$ was related to a faster time to diabetes than i-IFG$_{low}$. Finally, the time to incident diabetes of i-IFG$_{high}$ and i-IGT was similar.

In an additional analysis, we split i-IFG$_{low}$ (100–109 mg/dL) into two categories: i-IFG (100−104 mg/dL) and i-IFG (105–109 mg/dL). The RR in these groups was 1.57 (95% CI 0.86−2.87) and 2.80 (1.57−4.99), respectively; in the AFT model, e^{β} was 0.84 (0.69−1.04) and 0.72 (0.58−0.90), respectively.

Our study gives several insights. First, 10-year diabetes incidences >40% were only found in i-IFG$_{high}$ and in combined IFG/IGT (for both IFG$_{low}$ and IFG$_{high}$). Second, the OGTT is helpful for identifying high-risk groups for type 2 diabetes. For example, diabetes risk was much stronger in IFG$_{low}$ when IGT co-occurred. Third, among participants with i-IFG$_{low}$ only 15% progressed to diabetes, but as this group was large (prevalence 22%), the absolute number of persons with incident diabetes from this subgroup equaled the number from other prediabetes categories with higher diabetes risk. Generally, the numbers of incident diabetes cases were similar for all categories of glycemic status including NGT, indicating that population-based approaches should complement high-risk approaches in diabetes prevention. For all prediabetes categories, population-attributable risks lay between 0.18 and 0.27; the small range indicates again that all prediabetes

categories contribute similarly to the diabetes burden. Fourth, i-IFG (100–109 mg/dL) is not a homogenous category, and there is a strong increase in diabetes risk at the 105 mg/dL cut point. This is in line with results by Zhuo et al. (4), who did an economic analysis of fasting plasma glucose (FPG) thresholds and suggested a threshold of 105 mg/dL to identify persons at high risk of type 2 diabetes (4). Our data support model-based estimates in the U.S., which suggested that a great reduction in the absolute number of diabetes cases would be achieved through implementation of a structured lifestyle intervention in people with $IFG_{high/low}$ (5). However, it must be noted that evidence for lifestyle intervention mainly comes from studies of people with IGT rather than IFG. Finally, our study shows that all prediabetes categories have an unfavorable risk profile (e.g., obesity, hypertension). Thus, those affected are at a higher cardiovascular risk.

In conclusion, in our older cohort—for younger ones results may be different—we found that persons with fasting glucose values of 100 to <110 mg/dL have a twofold higher long-term risk to progress to diabetes than those with NGT and that i-IFG_{low} is almost three times more prevalent than i-IFG_{high} with implications for the expected number of incident diabetes cases in this population. Lowering FPG thresholds and including more people into prevention programs leads to a gain in quality-adjusted life years but also to an increase in costs and a reduction in cost-effectiveness. Therefore, selection of an FPG cut point depends on how many health care resources are accepted to be put toward prevention.

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