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ORIGINAL RESEARCH

Normal fasting plasma glycemia and risk of type 2 diabetes - Review of the evidence

D.ssa D. Iodice[1]

1 Biologist, Italy

1. ABSTRACT

The analyzed study evaluated whether differences in fasting plasma glycemia, even when below 100 mg/dL and therefore not diagnostic for diabetes, were associated with the subsequent development of type 2 diabetes. In an Italian retrospective cohort of 13,845 adults aged 40 to 69, followed for an average of approximately seven to eight years, the initial glycemia range between 91 and 99 mg/dL was associated with a higher incidence of diabetes compared to the 51-82 mg/dL range. After adjusting for available metabolic and behavioral factors, the hazard ratio—the ratio of the rate of disease onset in the compared groups—was 2.03.The research contributes to the passage from “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, according to which the high range of normoglycemia can represent a prognostic indicator, i.e., associated with the probability of a future clinical event. Independent studies in the United States, Japan, and China confirm that future risk increases progressively even before the diagnostic threshold. However, observational cohorts do not prove that glycemia is the sole cause of diabetes, nor that intervening exclusively on this value necessarily changes the clinical outcome. A non-linear relationship, with elevated risk even at very low values in a Japanese cohort, also suggests not interpreting the data as a simple linear scale applicable indiscriminately to every person.

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MISSION

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Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

2. ANALYZED STUDY

The research question was whether, among people without diabetes and with fasting glycemia below 100 mg/dL, values in the higher end of the normal range were associated with a higher probability of developing type 2 diabetes in subsequent years. The hypothesis was that the risk does not begin abruptly only beyond a diagnostic threshold, but increases even within the normoglycemic range.This question is directly relevant to section 2.4.1 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi. The book does not use the publication to claim that a glycemia of 91-99 mg/dL is equivalent to diabetes, but to support a more specific point: in the studied population, this range was associated with an increased future risk of diabetes compared to lower glycemic values.As a retrospective observational study, the research can identify associations and estimate their magnitude after statistical adjustment for certain known factors. However, it cannot prove that the glycemic value, on its own, causes diabetes, nor can it establish whether pharmacologically reducing or modifying the lifestyle to lower a single glycemic value in normoglycemic individuals prevents the disease.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors used retrospective data from the laboratory of the Desio Hospital in Lombardy. The study included 13,845 individuals—8,110 women and 5,735 men—aged between 40 and 69 years. At the time of inclusion, all participants had a fasting plasma glycemia level of less than 100 mg/dL. To be selected, they also had to have at least three additional glycemia measurements between 1992 and 2008, as well as blood lipid data.Individuals with requests for glycated hemoglobin—a test that reflects average glucose exposure over the preceding months—were excluded with the intent of reducing the inclusion of subjects already being evaluated for possible diabetes. Type 2 diabetes was defined by two fasting glycemia measurements greater than 125 mg/dL. Participants were divided into three initial ranges: 51–82, 83–90, and 91–99 mg/dL.Glycemia was measured using an enzymatic-colorimetric method within two hours of blood collection. The authors employed Cox models, a statistical analysis that compares the rate at which an event occurs over time, to calculate hazard ratios with 95% confidence intervals. In a random subgroup of 3,593 people, additional data obtained via questionnaire were available, including body mass index, hypertension, family history of diabetes, smoking, and alcohol consumption. The final model adjusted for these factors was therefore conducted only within this subgroup.

4. RESULTS

During 108,061 person-years of observation, which is the sum of the follow-up periods for all participants, 307 incident cases of type 2 diabetes occurred. The mean follow-up was 7.9 years for women and 7.4 years for men. The incidence increased as initial glycemia values rose, even while remaining below 100 mg/dL.In women, the percentage of new cases increased from 0.75% in the 51-82 mg/dL range to 3.37% in the 91-99 mg/dL range. In men, it increased from 0.58% to 4.08%. In other words, more new cases of diabetes were observed during follow-up in the highest range of normoglycemia compared to the lowest range.After adjusting for age, participants in the 91-99 mg/dL range showed a hazard ratio of 2.89 for women and 2.87 for men compared to the 51-82 mg/dL range. Further adjustment for triglycerides and cholesterol had little effect on these estimates. In the final model, which also included body mass index, hypertension, family history, smoking, and alcohol in the subgroup with complete data, the 91-99 mg/dL range maintained a hazard ratio of 2.03, with a 95% confidence interval from 1.18 to 3.50.This indicates that, in the available data, the 91-99 mg/dL range was associated with a rate of diabetes onset approximately double that of the lowest glycemic range. For the intermediate range, the final model reported a hazard ratio of 1.42 with a confidence interval from 0.42 to 4.74: a very wide interval that includes 1, and is therefore also compatible with the absence of a statistically clear difference. The text also contains a discrepancy between the intermediate range initially defined as 83-90 mg/dL and the one reported in the final model as 86-90 mg/dL.

5. INTERPRETATION

In simple terms, the study suggests that fasting glycemia still below the diagnostic threshold for prediabetes may contain information about future metabolic risk. The result does not imply that every person with 91-99 mg/dL will develop diabetes. Instead, it indicates that, in the observed cohort, this range was associated with a higher future frequency of diabetes compared to lower values.The segment of the book's narrative that is effectively documented is therefore: fasting glycemia in the high range of normoglycemia higher future risk of type 2 diabetes. The study does not directly measure insulin sensitivity—that is, the ability of tissues to respond to insulin—nor the function of pancreatic beta cells, which produce insulin. It may therefore be consistent with early metabolic alterations, but it does not demonstrate which biological mechanism produced the association.Adjustment for certain risk factors strengthens the prognostic interpretation of the glycemic value, but does not completely eliminate the possible effect of unmeasured or incompletely measured factors. The limitations of the selection are also relevant: these are people who had repeated laboratory tests, came from a specific geographic area, and had detailed clinical data available for only a portion of the sample. The result should therefore be read as observational evidence of risk stratification, not as an independent diagnostic or therapeutic indication.

6. INDEPENDENT SUPPORTING EVIDENCE

Direct confirmation of this same narrative comes from a U.S. cohort of 46,578 adults without diabetes and with an initial glycemia of less than 100 mg/dL. After adjusting for age, sex, body mass index, blood pressure, lipids, smoking, and other conditions, each 1 mg/dL increase in fasting glycemia was associated with a 6% increase in the rate of diabetes diagnosis. Compared to values below 85 mg/dL, the 95-99 mg/dL range was associated with a hazard ratio of 2.33, with a 95% confidence interval from 1.95 to 2.79. This study directly confirms the passage in the book stating that the high end of normoglycemia signals a higher future risk [1].Another cohort, consisting of 13,163 Israeli men aged between 26 and 45 years and followed from 1992 to 2004, observed a progression of risk starting as early as glycemia levels of 87 mg/dL or higher, compared to the quintile with values below 81 mg/dL. The model was adjusted for age, family history, body mass index, physical activity, smoking, and triglycerides. This evidence is particularly useful because it shows the same direction of association in younger adults and in a different geographical context; however, it remains limited to the male population [2].In the Panasonic cohort, 37,148 Japanese workers who were initially normoglycemic were followed from 2008 to 2018, and 1,028 developed diabetes. Between 90 and 99 mg/dL, each 1 mg/dL increase was associated with a 9.0% increase in the risk of developing diabetes. Compared to a glycemia of 89 mg/dL or lower, the hazard ratios increased progressively up to 3.41 for the 98-99 mg/dL range. The gradient was also present in people with obesity, suggesting that the association did not depend exclusively on excess weight [3].A more recent analysis examined two Asian cohorts: 204,640 people in China and 15,464 in Japan. The relationship between initial normal glycemia and future diabetes did not appear perfectly linear, but rather J-shaped. The risk increased more rapidly beyond inflection points estimated at around 81 mg/dL in the Chinese cohort and 94 mg/dL in the Japanese one. This result confirms the book's central idea—that risk can increase before diagnostic thresholds—but clarifies that the shape of the relationship may vary between populations [4].

7. CONFLICTING EVIDENCE

No sufficiently relevant directly conflicting evidence has been identified that denies the association between fasting glycemia in the high-normal range and an increased future risk of diabetes. However, there is data that complicates the idea of a linear trend in which every lower value is necessarily associated with lower risk.In a Japanese national cohort of 186,749 people without diabetes, followed for three years, the risk of new-onset diabetes was found to be increased both with glycemia levels between 90 and 125 mg/dL and with values below 70 mg/dL, compared to the 85-89 mg/dL range. This finding does not contradict the increased risk in the high-normal range, but it shows a J-shaped relationship and suggests that very low values may identify different biological or clinical conditions [5].This observation requires caution. Fasting glycemia is an indicator influenced by actual

fasting, acute conditions, liver function, medications, body composition, and analytical variability. Furthermore, differences between studies in the definition of diabetes, participants, duration of follow-up, and variables considered can alter risk estimation. Therefore, the glycemic value must be interpreted together with the overall clinical picture, not as an isolated measure capable of defining an individual's metabolic fate on its own.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study under review from independent research that confirms or provides context for the passage in the book.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Retrospective cohort	13,845 Italian adults, 40-69 years old	Glycemia of 91-99 mg/dL associated with an HR of 2.03 for diabetes compared to 51-82 mg/dL in the subgroup with complete data	direct confirmation	moderate
[1]	Retrospective observational cohort	46,578 normoglycemic US adults	Each 1 mg/dL associated with an HR of 1.06; glycemia of 95-99 mg/dL associated with an HR of 2.33 compared to less than 85 mg/dL	direct confirmation	moderate
[2]	Observational cohort	13,163 Israeli men, 26-45 years old	Progressively higher risk from 87 mg/dL compared to values below 81 mg/dL	direct confirmation	moderate
[3]	Retrospective cohort	37,148 normoglycemic Japanese workers	Between 90 and 99 mg/dL, each 1 mg/dL increase associated with a 9% increase in diabetes risk	direct confirmation	moderate
[4]	Two observational cohorts	204,640 people in China and 15,464 in Japan	J-shaped relationship; more rapid risk increase above approximately 81 mg/dL in China and 94 mg/dL in Japan	indirect confirmation	moderate
[5]	Observational cohort	186,749 Japanese adults without diabetes	Increased risk both at 90-125 mg/dL and below 70 mg/dL compared to 85-89 mg/dL	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study appropriately supports the claim that the high end of fasting glycemia, even if below 100 mg/dL, may be associated with a higher future probability of type 2 diabetes. The association was observed in an Italian population and confirmed by independent cohorts in other countries.

The evidence is quite well-supported from a prognostic standpoint: a higher glycemic value within the normal range identifies, on average, a group at higher risk. However, it does not prove that the value is the sole cause of the disease, nor that a single measurement allows for a diagnosis, a certain individual prognosis, or a therapeutic choice. Furthermore, the relationship appears non-linear in some populations and requires interpretation in the context of other clinical and metabolic factors.

Aggiornato al 17/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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