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ORIGINAL RESEARCH

Fasting glycemia and risk of type 2 diabetes: evidence from two cohort studies

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1. ABSTRACT

The analyzed study examined whether fasting plasma glycemia, even when within the range considered normal, was associated with the subsequent onset of type 2 diabetes. It brought together two observational cohorts from China and Japan, totaling 220,104 adults, and identified 2,611 new cases of diabetes during the follow-up. The analysis showed a J-shaped relationship: in the upper part of the normal range, the increase in glycemia was associated with a more rapid increase in the future risk of diabetes.The publication contributes to the passage from “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, according to which fasting glycemia can function as a continuous biomarker of risk, not just as a diagnostic threshold. Independent US, Italian, and Japanese cohorts report consistent associations in the high range of normoglycemia. Precise thresholds, however, vary between populations and clinical settings; the data are therefore prognostic and do not demonstrate that pharmacologically lowering normal values prevents diabetes.

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MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

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 differences in fasting plasma glycemia, even when they do not reach the diagnostic criteria for prediabetes or diabetes, could signal a different probability of developing type 2 diabetes in subsequent years. The hypothesis was that the risk does not follow a simple straight line and that it could increase more rapidly beyond certain values still classified as normal.The relevance to the section "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is specific: the study documents the observational segment of the narrative according to which fasting glycemia is not just a fixed value useful for diagnosis, but an indicator associated in a gradual way with future risk. It does not, however, demonstrate that a specific glycemia value directly causes diabetes, nor does it identify which intervention reduces the risk in normoglycemic individuals.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The research combined two cohort studies, which are groups of people followed over time without assigning treatments. The Chinese cohort included participants who underwent health check-ups at 32 facilities in 11 cities between 2010 and 2016. The Japanese cohort came from the NAGALA study, conducted at the Murakami Memorial Hospital between 1994 and 2016. After exclusions, 220,104 adults were analyzed: 204,640 Chinese and 15,464 Japanese.Fasting plasma glycemia was measured after at least eight hours without food intake. Data were also collected on age, sex, body mass index or BMI (ratio of weight to height), blood pressure, total cholesterol, triglycerides, alanine aminotransferase or ALT (an enzyme that can reflect liver alterations), smoking, and alcohol consumption. Incident type 2 diabetes was defined by fasting glycemia equal to or greater than 7.0 mmol/L, glycated hemoglobin equal to or greater than 6.5%, or a diagnosis reported by the participant.Annual check-ups constituted the follow-up. The authors used Cox models, an analysis that estimates the association between an initial characteristic and the rate at which an event occurs over time, and restricted cubic splines, a method useful for verifying whether the relationship changes slope across different glycemia values. The complete models were adjusted for numerous potential confounding factors. The full inclusion and exclusion criteria illustrated in the flowchart are not reported in the available textual material.

4. RESULTS

The average age of the 220,104 participants was 41.8 years. The Chinese cohort was followed for an average of 3.13 years, and the Japanese cohort for 6.05 years. During this period, 2,611 cases of type 2 diabetes occurred: 2,238 in China and 373 in Japan. Individuals in the highest quintile of baseline glycemia also had higher average age, BMI, blood pressure, triglycerides, and ALT compared to the groups with lower glycemia. This shows that glycemia was accompanied by other unfavorable metabolic factors, which is why statistical adjustment was necessary.After this adjustment, higher fasting glycemia was associated with a higher incidence of diabetes. When comparing quintiles, the highest quintile had a hazard ratio (HR) of 8.07 compared to the lowest quintile across the combined cohorts. The HR expresses the ratio of the rate at which the event occurs in the groups being compared: in this case, it indicates a higher rate of diabetes onset in the group with higher baseline glycemia. The 95% confidence interval was 6.82-9.56, and the P-value was less than 0.001.The result most relevant to the book comes from the non-linear analysis. In the Chinese cohort, above 4.5 mmol/L, equivalent to approximately 81 mg/dL, every increase in glycemia was associated with a rapid increase in the risk of diabetes, with an HR of 7.30 and a confidence interval of 6.53-8.17. In the Japanese cohort, the inflection point was 5.2 mmol/L, approximately 94 mg/dL, and above this, the HR was 21.13, with a confidence interval of 13.17-33.91. Below these points, the association was not statistically significant in the segmented model.The ability of baseline glycemia to distinguish who would later develop diabetes, measured by the area under the ROC curve, was 0.762 in China and 0.805 in Japan. A value close to 1 would indicate perfect discrimination; these results indicate fair predictive ability, but not enough to turn glycemia alone into a certain individual diagnosis. Furthermore, the differences between the inflection points of the two cohorts indicate that a single threshold cannot be considered universal.

5. INTERPRETATION

In simple terms, the study shows that two people without diabetes who both have formally normal glycemia levels do not necessarily have the same probability of being diagnosed with diabetes in the following years. In the cohorts considered, the probability increased especially when the initial value was in the higher range of normal.The point supported by the publication is therefore: normal but higher fasting glycemia higher observed risk of type 2 diabetes during follow-up. This is consistent with the use of glycemia as a prognostic biomarker, that is, as an indicator associated with the likely future course, rather than as a predictive biomarker for response to a treatment.The authors discuss possible contributions of insulin resistance and reduced insulin secretion. Insulin resistance is the reduced ability of tissues to respond to insulin; reduced secretion indicates a lower capacity of pancreatic beta cells to produce the hormone. However, these alterations were not measured directly in the study and remain biologically plausible interpretations, not results demonstrated by the cohort. Furthermore, residual confounding, variations in glycemia over time, and diagnoses not systematically based on the oral glucose tolerance test may have influenced the estimates.

6. INDEPENDENT CONFIRMING EVIDENCE

A large U.S. cohort has provided direct confirmation of this central transition. Nichols, Hillier, and Brown followed adults who were initially diabetes-free, categorizing fasting glycemia into ranges from less than 85 mg/dL to 95-99 mg/dL. After adjusting for age, sex, BMI, blood pressure, lipids, smoking, cardiovascular disease, and hypertension, each 1 mg/dL increase in glycemia was associated with a 6% increase in the risk of a diabetes diagnosis. The 95-99 mg/dL range was associated with an HR of 2.33 compared to values below 85 mg/dL. This is an independent observational confirmation of the association in the high-normal range of glycemia, but it does not prove a causal relationship [1].In a Mediterranean cohort of 13,845 apparently healthy adults, Brambilla and colleagues observed 307 new cases of diabetes over 108,061 person-years of observation. Compared to a glycemia of 51-82 mg/dL, values of 91-99 mg/dL were associated with an adjusted HR of 2.03, with a confidence interval of 1.18-3.50. The direction of the effect is therefore the same: in the upper end of the normal range, the future risk of diabetes was higher. However, the number of events was lower than in the previously analyzed study, and the population was aged between 40 and 69 years [2].The Panasonic cohort added a particularly relevant finding in Japan. Among 37,148 individuals with normal glycemia followed from 2008 to 2018, 1,028 developed diabetes. Between 90 and 99 mg/dL, each 1 mg/dL increment was associated with a 9% increase in risk. Compared to values equal to or less than 89 mg/dL, the 98-99 mg/dL range was associated with an HR of 3.41, with a confidence interval of 2.79-4.15. Even in participants with obesity, the increasing gradient remained present. This study confirms that the observed phenomenon does not depend exclusively on excess weight, although it does not eliminate all possible confounding factors [3].

7. CONFLICTING EVIDENCE

No sufficiently relevant directly conflicting evidence has been identified that shows, in normoglycemic individuals, a reduction in diabetes risk as glycemia increases within the high end of the range. However, there is data that suggests caution when interpreting identical inflection points for everyone.In a Japanese national cohort of 186,749 people without diabetes, Ogata and colleagues observed an increased probability of incident diabetes both with glycemia of 90-125 mg/dL and with values below 70 mg/dL, compared to the reference category of 85-89 mg/dL. In people with previous cardiovascular disease, however, the increase was evident primarily from 95 mg/dL onwards. This does not contradict the general association between high-normal glycemia and diabetes, but it indicates that the shape of the curve, the minimum risk value, and the apparent threshold can depend on clinical history, age, study design, and diagnostic method [4].

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study under review from the independent cohorts used to verify the narrative of the paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Two observational cohorts	220,104 adults in China and Japan	Within the normal range, the risk of diabetes increased more rapidly above approximately 81 mg/dL in China and 94 mg/dL in Japan.	direct confirmation	moderate
[1]	Observational cohort	US adults without diabetes	Each 1 mg/dL increase raised the risk by 6%; 95-99 mg/dL: HR 2.33 compared to less than 85 mg/dL.	direct confirmation	moderate
[2]	Observational cohort	13,845 Mediterranean adults, 40-69 years old	91-99 mg/dL associated with HR 2.03 for diabetes compared to 51-82 mg/dL.	direct confirmation	moderate
[3]	Retrospective cohort	37,148 Japanese workers with normal glycemia	Between 90 and 99 mg/dL, every 1 mg/dL was associated with a 9% increase in diabetes risk.	direct confirmation	moderate
[4]	Observational cohort	186,749 Japanese adults without diabetes	Risk increased both below 70 mg/dL and from 90 mg/dL, but in people with cardiovascular disease from 95 mg/dL.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication appropriately supports the idea that the future risk of diabetes does not necessarily begin suddenly upon exceeding diagnostic thresholds. In the cohorts considered, higher fasting glycemia values within the normal range were associated with a higher subsequent incidence of diabetes, with a non-linear relationship.The narrative is confirmed by independent evidence from the United States, Italy, and Japan. It remains essential to distinguish prognostic value from causality: high-normal glycemia identifies a higher probability of future diabetes, but it does not by itself demonstrate already inevitable metabolic deterioration, nor does it indicate a specific treatment. The observed thresholds require validation in other populations and with repeated glycemic measurements.

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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