

# Type 2 diabetes: Gut bugs predict risk before blood sugar rises?

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Type 2 diabetes is currently diagnosed by testing blood sugar directly, HbA1c, fasting glucose, or an oral tolerance test, which means someone with completely normal readings gets no early warning even if they are on a trajectory toward the disease. A large new analysis presented at the EASD Annual Meeting in Milan asks whether the gut microbiome could fill that gap, detecting risk before blood sugar itself changes.

## KEY TAKEAWAYS

- **The Pivot:** A gut bacterial signature linked to type 2 diabetes is already detectable in people with entirely normal blood sugar, tracking post-meal glucose response before any diagnostic threshold is crossed.
- **The Data:** 789 species were associated with type 2 diabetes, and the same pattern correlated strongly (Spearman  $\rho=0.69$ ) with post-meal glucose response in 135,093 people with normal blood sugar.
- **The Action:** The authors position this as an add-on to, not a replacement for, standard risk factors and diagnostic tests, for identifying who might benefit most from early lifestyle intervention.

Dr Gabriel Baldanzi and Professor Nicola Segata at the University of Trento, working with colleagues at Zoe Ltd and King's College London, analysed metagenomic data (the DNA sequences of gut bacteria) and health records from 229,025 participants in the PREDICT 3 study, including 3,687 with type 2 diabetes and 14,022 with prediabetes. Species-level associations were adjusted for age, sex and BMI, and separately checked in people using versus not using glucose-lowering medication.

## 789 species linked to diabetes, hundreds showing up before diagnosis

The researchers identified 789 bacterial species significantly associated with type 2 diabetes, 168 more abundant and 621 less abundant in people with the condition. The pattern was not simply a side effect of diabetes medication, regression coefficients were strongly correlated (Spearman  $\rho=0.83$ ) between medicated and unmedicated people with diabetes, though larger in the medicated group. Of the 789 species, 587 were also significantly associated with prediabetes in people not on glucose-lowering medication, and 523 were linked to a positive family history of diabetes in people with entirely normal blood sugar.

Species named in the analysis include *Enterocloster boltea*, more abundant in people with type 2 diabetes and previously linked to poorer cardiovascular and metabolic health, and *Romboutsia timonensis*, less abundant in type 2 diabetes and only formally described within the last decade. Some of the identified species have never been isolated or cultured in a laboratory at all, "new to science," in the words of Professor Segata, and were found only through analysing the metagenomic data directly.

## The signature tracks post-meal blood sugar, even without a diagnosis

In 135,093 participants with entirely normal blood sugar, the researchers measured post-meal glucose response directly using continuous glucose monitors, the two-hour incremental area under the curve after a standardised meal, a marker of emerging insulin resistance. The bacterial coefficients associated with type 2 diabetes were strongly correlated with the coefficients associated with this post-meal glucose response (Spearman  $\rho$  0.69), meaning the same microbial signature that marks existing diabetes also tracks a subtler, pre-diagnostic marker of insulin resistance in people with normal blood tests.

"Identifying these clear microbial changes before blood sugar levels worsen could lead to earlier intervention with food and lifestyle choices, as well as treatment options, to prevent T2D," said Professor Tim Spector, a study co-author and ZOE's scientific co-founder. Several co-authors, including Spector, are ZOE co-founders, employees, consultants or equity holders in the company, whose commercial gut-health products this research is directly relevant to; the study drew on ZOE's PREDICT cohort. The authors state microbiome testing should complement, not replace, standard diagnostic tests.

The study's findings underscore the potential for gut microbiome analysis to serve as an early risk stratification tool, complementing traditional metabolic assessments. While the strong correlation between microbial signatures and both established type 2 diabetes and subtle post-meal glucose dysregulation is compelling, it is crucial to acknowledge the observational nature of this large-scale cohort study. The identified associations do not definitively establish causality; rather, they highlight a robust correlative link that warrants further investigation through interventional studies. Future research could explore whether targeted microbiome modulation, perhaps through dietary interventions or specific probiotic/prebiotic regimens informed by these signatures, could prevent or delay the progression from prediabetes to type 2 diabetes.

One of the study's strengths lies in its extensive dataset, encompassing a diverse population and leveraging advanced metagenomic sequencing. However, the reliance on a single cohort (PREDICT 3) means that external validation in independent and ethnically diverse populations will be essential to confirm the generalizability of these microbial signatures. Furthermore, while adjustments were made for key confounders like age, sex, and BMI, other lifestyle factors, dietary habits, and environmental exposures that significantly influence the gut microbiome were not exhaustively accounted for in the primary analysis. These unmeasured variables could potentially influence both microbiome composition and diabetes risk, introducing residual confounding.

The identification of "new to science" species highlights the ongoing frontier of microbiome research and the limitations of traditional culture-dependent methods. This emphasizes the value of metagenomic approaches in uncovering the full diversity of the gut ecosystem. For healthcare professionals, these findings suggest a future where gut microbiome profiling could become an integral part of personalized risk assessment for metabolic diseases. While not yet a standalone diagnostic tool, understanding a patient's microbial signature could inform more proactive and tailored preventative

strategies, particularly for individuals with a family history of diabetes or those exhibiting early signs of insulin resistance, even before overt hyperglycemia manifests. This could involve personalized nutritional guidance aimed at fostering a more protective gut environment, potentially delaying or even preventing the onset of type 2 diabetes.

#### CLINICAL IMPLICATIONS

The scale here, 229,025 people and a cross-check against directly measured post-meal glucose response in a separate 135,093-person subset, is substantially larger than prior microbiome-diabetes studies, which the authors note have previously disagreed on which specific bacterial species matter. That consistency check against an objective physiological measure, not just diagnosis codes, is a genuine methodological strength. This is an association study: it cannot establish whether these bacterial shifts cause insulin resistance, result from it, or both feed into a shared upstream driver like diet. The authors themselves frame the value as motivational and risk-stratifying, "if we can detect early shifts in the gut microbiome and show someone they are on the right track, that could be a powerful source of motivation," in Dr Baldanzi's words, rather than diagnostic.

The ZOE co-authorship and financial ties are extensive and clearly disclosed, several authors hold company equity or options, and the underlying PREDICT cohort is ZOE's own commercial research platform. That doesn't invalidate the metagenomic findings, but it's directly relevant given ZOE sells gut-health and metabolic testing products to consumers, and this research supports the premise behind them.

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#### REFERENCES

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