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Fasting Ketone Bodies and Incident Type 2 Diabetes in the General Population

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With rising incidence and prevalence of type 2 diabetes, prevention including identification of prospective biomarkers becomes increasingly relevant. Although ketone bodies recently received a renewed interest as potential biomarkers, data linking these metabolites to diabetes risk are scarce. Therefore, the present prospective study investigated a potential association between fasting ketone bodies and incident type 2 diabetes in the general population. This study from the PREVEND cohort included 3,307 participants from the general population initially free of diabetes or impaired fasting glucose. Baseline fasting ketone body concentrations were measured by nuclear magnetic resonance spectroscopy. One hundred twenty-six participants (3.8%) developed type 2 diabetes during a median (interquartile range) follow-up of 7.3 (6.3–7.6) years. In Kaplan-Meier analysis, sex-stratified ketone body levels strongly positively associated with incident type 2 diabetes, which was confirmed in Cox regression analyses adjusted for several potential confounders. There was no significant interaction by sex. Both 3-β-hydroxybutyrate and acetoacetate+acetone individually associated with incident type 2 diabetes. In conclusion, fasting plasma ketone body levels are strongly positively associated with incident type 2 diabetes in the general population independent of several other recognized risk factors. These results may have important implications for diabetes prevention including dietary strategies.

Incidence and prevalence of type 2 diabetes are rising with high associated healthcare and societal costs (1,2). Preventive strategies to change this trajectory include

ARTICLE HIGHLIGHTS

- The identification of biomarkers that predict type 2 diabetes is increasingly relevant for personalized medicine strategies.
- Data regarding ketone bodies and incident type 2 diabetes are scarce.
- This study shows that ketone bodies, either combined or as individual subspecies, are strongly associated with incident type 2 diabetes in the general population, independent of potential confounders.
- These results may have important implications for diabetes prevention including dietary strategies.

identification of predictive biomarkers combined with early interventions (2).

Ketone bodies are an alternative energy source to glucose during fasting produced from fatty acids. Primarily, 3-β-hydroxybutyrate (3HB) and acetoacetate (AcAc) are formed, and, secondarily, acetone, a spontaneous breakdown product of AcAc (3). Insulin regulates ketogenesis, with low insulin levels stimulating it (3,4). Of note, in insulin resistance, the ability of insulin to suppress ketogenesis appears maintained (5).

In heart failure, higher circulating ketone body levels associated with better outcomes (4). Further, treatment with sodium–glucose cotransporter 2 inhibitors, which improve glycemic control and, very efficiently, diabetic complications, increased circulating ketone bodies (6,7). Although not part of contemporary nutritional guidelines, so-called ketogenic

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diets, high in fats and very low in carbohydrates, that result in measurably higher ketone body levels are vividly discussed as a potential strategy to prevent type 2 diabetes (8). However, data on a potential association between ketone bodies and incident type 2 diabetes in the general population are scarce. Therefore, the current study investigated the relationship between baseline plasma ketone bodies and de novo type 2 diabetes in a large general population cohort.

RESEARCH DESIGN AND METHODS

Prevention of REnal and Vascular ENd-stage Disease (PREVEND) is a prospective longitudinal cohort study from the north of the Netherlands (9). Briefly, from initially screened 8,592 participants (1997–1998), 6,893 returned for the second screening (2001–2003, baseline of the current study). We excluded subjects with nonfasting laboratory measurements, with missing data of ketone bodies or diabetes follow-up, with ketone body levels <2.5th percentile and >97.5th percentile, or with preexisting diabetes (10) or impaired fasting glucose (11), leaving 3,307 participants. Type 2 diabetes was defined as fasting glucose of ≥7.0 mmol/L, nonfasting glucose of ≥11.1 mmol/L, self-report of type 2 diabetes diagnosis, or initiation of glucose-lowering medication (10). Impaired fasting glucose was defined according to World Health Organization criteria reflecting standard of care in the Netherlands (6.1–7.0 mmol/L) (11).

This study was approved by the local medical ethical committee (Groningen, the Netherlands, MEC96/01/022) and carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Outcome and End Point
The main predictor was circulating ketone body levels. The study end point was incident type 2 diabetes. Follow-up was defined as the time period between baseline measurements and type 2 diabetes diagnosis or end of the observation period.

General Participant Characteristics
Participants attended two outpatient visits during which baseline data were collected, including general participant characteristics such as lifestyle parameters and medication use. Longitudinal information of medication use was obtained from the pharmacy dispensing registry.

Laboratory Measurements
Venous plasma was drawn after an overnight fast. Glucose and total cholesterol were determined using dry chemistry (Eastman Kodak, Rochester, NY), urinary albumin and high sensitivity C-reactive (hsCRP) protein concentrations utilizing nephelometry (Dade Behring Diagnostic, Marburg, Germany), and insulin by immunoturbidimety (Diazyme Laboratories, Poway, CA). Ketone bodies (AcAc, 3HB, acetone) and triglycerides were determined by nuclear magnetic resonance (NMR) spectroscopy at Labcorp (Morrisville, NC). NMR spectra were

collected on Vantera Clinical Analyzers (12), and concentrations were calculated using an optimized NMR LipoProfile test version (LP4 algorithm) as described (13). HDL cholesterol was assessed using a homogenous method (direct HDL; Abbott Laboratories, Abbot Park, IL). Serum creatinine was measured enzymatically, and serum cystatin C was measured by immunoassay (Gentian AS, Moss, Norway), both on a Roche Modular Analyzer (Roche Diagnostics, Mannheim, Germany). Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) combined creatinine-cystatin C equation. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as fasting plasma insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5. LDL cholesterol was determined using the National Institutes of Health equation (all participants had triglycerides below 800 mg/dL) (14).

Statistical Analysis
All statistical analyses were done using R Studio (RStudio Team, 2020). P values below 0.05 were considered significant. χ^2 test was used for categorical variables (total numbers [%]), Kruskal-Wallis test for skewed continuous variables (median [interquartile range (IQR)]). Normal distribution was checked by Shapiro-Wilk test. Multivariate linear regression with backward elimination was used to define baseline variables independently correlated to ketone bodies. Kaplan-Meier curves were constructed based on tertiles of ketone bodies; significance was determined utilizing the log-rank test. To assess the continuous relationship between ketone bodies and incident type 2 diabetes, log2-transformed ketone body concentrations were used, adjusted for age and sex. Prospective associations between baseline ketone bodies and incident type 2 diabetes were explored with Cox regression analysis. Schoenfeld residuals test showed that the proportional hazard assumption was not violated. First, crude analysis (model 1) was carried out and hazard ratios (HR) (95% CI) were obtained for log2-transformed ketone bodies. Subsequently, we adjusted the crude model stepwise for the indicated parameters. To explore differential associations of different ketone bodies with type 2 diabetes, Cox regression analyses were repeated. AcAc and acetone were combined because of the spontaneous formation of acetone from AcAc. Subgroup analyses with interaction tests were performed to determine HR across categories of baseline characteristics using, for continuous variables, median values as the cutoff.

Data and Resource Availability
The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

RESULTS

Out of 3,307 participants, 126 (3.8%) developed type 2 diabetes during a median follow-up [IQR] of 7.3 [6.3–7.6] years. The median ketone body level in all participants was 175.5 [139.5–241.1] μmol/L. Among subjects developing

type 2 diabetes during follow-up, median ketone body levels were 200.1 [161.2–264.4] vs. 174.8 [138.9–239.4] μmol/L in participants who stayed free of type 2 diabetes ($P < 0.001$).

Analysis of baseline participant level characteristics (Table 1) indicated that subjects in the higher tertiles of ketone bodies were older ($P < 0.001$) and past smokers ($P = 0.022$). BMI ($P < 0.001$), waist circumference ($P < 0.001$), glucose ($P < 0.001$), HOMA-IR ($P < 0.001$), triglycerides ($P < 0.001$), and systolic blood pressure ($P = 0.012$) were significantly increased in the medium and high tertiles, while HDL cholesterol ($P = 0.003$) was decreased. Subjects with higher ketone bodies had higher hsCRP ($P < 0.001$). Furthermore, participants in the low tertile had better kidney function (eGFR, $P < 0.001$) and less urinary albumin excretion ($P = 0.019$). Lastly, subjects with higher ketone bodies used lipid-lowering ($P = 0.015$) and antihypertensive medication ($P = 0.013$) more frequently. In linear regression with backward elimination (Supplementary Table 1), age (standardized β [95% CI] 5.39 [0.33, 10.46], $P = 0.037$), glucose (−4.74 [−8.46, −1.02], $P = 0.013$), and total cholesterol (−3.79 [−7.44, −0.13], $P = 0.042$) remained significantly associated with continuous fasting ketone body concentrations.

Kaplan-Meier analysis (Fig. 1) showed that higher tertiles of ketone bodies were significantly associated with incident type 2 diabetes ($P < 0.001$). Cox regression analysis (Table 2) demonstrated that high baseline fasting ketone body concentrations entailed higher type 2 diabetes incidence (model 1, $P < 0.001$). Adjusting for age and sex (model 2, $P = 0.001$), metabolic syndrome constituents and BMI (model 3, $P = 0.001$), HOMA-IR (model 4, $P = 0.001$), lipid-related biomarkers (model 5, $P = 0.001$), and renal function (model 6, $P = 0.002$) did not materially weaken this association. When adjusting baseline ketone bodies for changes in weight, smoking habits, and age during follow-up, the association with incident type 2 diabetes remained (HR 1.78 [1.27–2.48], $P = 0.001$). Neither total nor individual ketone bodies correlated with HOMA-IR ($r < 0.02$), and no significant interaction between HOMA-IR and ketone bodies for incident type 2 diabetes was detected ($P = 0.785$). Stratified analyses by several baseline-level characteristics revealed no significant interactions for the association between ketone bodies and incident diabetes (Supplementary Fig. 1). In addition, visualizing this prospective association continuously over the full range of ketone bodies (Fig. 2) showed an increase in the adjusted

Table 1—Baseline participant level characteristics according to tertiles of fasting ketone body levels

	Low tertile (n = 1,103) (<153.3 μmol/L)	Medium tertile (n = 1,103) (>153.3 to <211.5 μmol/L)	High tertile (n = 1,101) (>211.5 μmol/L)	P value
Ketone bodies (μmol/L)	126.7 [111.3–139.5]	175.5 [162.0–192.5]	284.3 [241.4–367.5]	<0.001
Type 2 diabetes during follow-up (%)	1.8	4.3	5.4	<0.001
Age (years)	50.3 [43.2–58.7]	53.3 [45.5–63.6]	53.5 [45.4–63.9]	<0.001
Female (%)	54.5	54.6	54.5	0.999
Intoxication				
Alcohol use (%)	73.5	75.2	77.3	0.121
Smoking (%)	28.5	26.9	28.5	0.640
Past smoking (%)	58.7	65.3	60.7	0.022
Metabolic health				
BMI (kg/m^2)	25.5 [23.3–28.1]	26.4 [24.1–29.2]	26.1 [23.6–29.0]	<0.001
Waist circumference (cm)	89.0 [81.0–98.0]	92.0 [84.0–100.0]	91.0 [82.0–100.0]	<0.001
Glucose (mmol/L)	4.7 [4.4–5.1]	4.8 [4.4–5.2]	4.7 [4.4–5.1]	<0.001
HOMA-IR	1.6 [1.1–2.3]	1.8 [1.3–2.8]	1.7 [1.1–2.6]	<0.001
hsCRP (mg/dL)	1.0 [0.5–2.0]	1.6 [0.7–3.3]	1.7 [0.7–3.8]	<0.001
Systolic blood pressure (mmHg)	121.0 [111.0–134.0]	122.0 [112.0–136.5]	123.0 [111.0–137.0]	0.012
Diastolic blood pressure (mmHg)	72.0 [66.0–79.0]	73.0 [67.0–79.0]	73.0 [67.0–79.5]	0.056
Lipid markers				
Total cholesterol (mmol/L)	5.3 [4.7–6.1]	5.5 [4.8–6.2]	5.4 [4.7–6.2]	0.012
HDL cholesterol (mmol/L)	1.3 [1.1–1.5]	1.2 [1.0–1.4]	1.2 [1.0–1.5]	0.003
LDL cholesterol (mmol/L)	3.5 [3.0–4.2]	3.7 [3.1–4.3]	3.6 [3.0–4.2]	0.225
Triglycerides (mg/dL)	90.0 [65.8–124.0]	108.5 [78.0–151.9]	99.1 [71.5–146.5]	<0.001
Renal function				
Serum creatinine (mmol/L)	70.0 [62.0–79.0]	70.0 [61.0–79.0]	71.0 [62.0–81.0]	0.104
eGFR (mL/min/1.73m^2)	95.0 [85.1–104.9]	93.7 [81.3–104.1]	92.8 [80.7–102.6]	<0.001
Urinary albumin excretion	5.1 [3.1–9.2]	5.7 [3.3–10.8]	5.4 [3.2–11.2]	0.019
Medication use				
Lipid lowering drugs (%)	6.7	9.8	7.2	0.015
Antihypertensives (%)	17.3	22.3	20.3	0.013

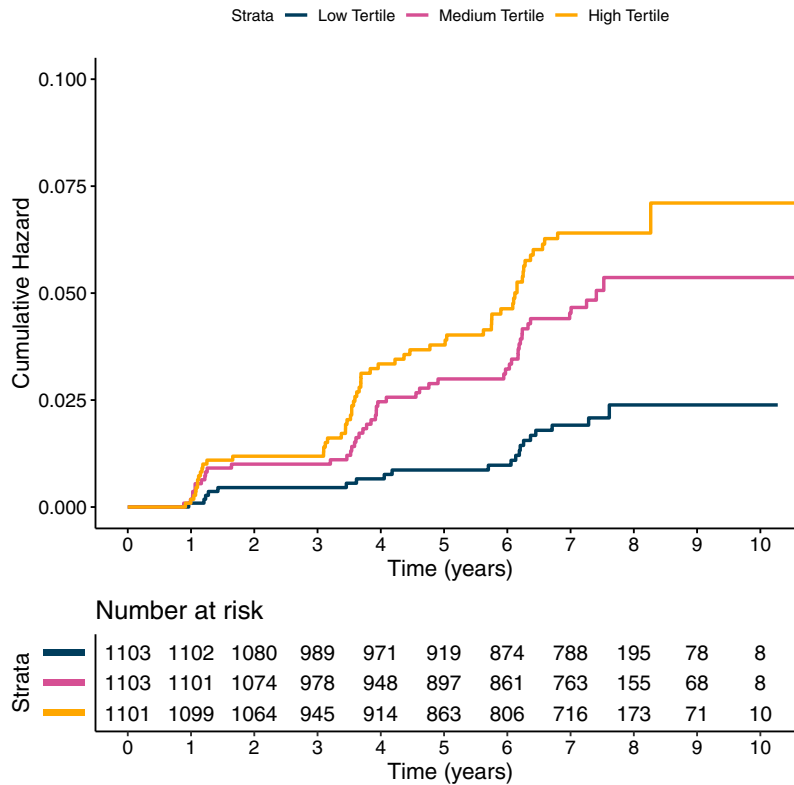Data are median [IQR] unless otherwise specified.

Figure 1—Kaplan-Meier analysis of type 2 diabetes incidence according to tertiles of ketone bodies (log-rank test, $P < 0.001$).

HR of type 2 diabetes with increasing fasting ketone body concentrations.

In separate Cox regression analyses either individually investigating levels of the ketone body subspecies AcAc + acetone and 3HB (Supplementary Table 2) or using very large triglyceride-rich lipoprotein particle concentration as a more objectifiable parameter for fasting (Supplementary Table 3), all models remained significant.

DISCUSSION

The results of this longitudinal prospective study demonstrate that fasting plasma ketone body levels strongly positively associate with incident type 2 diabetes in the general population independent of several recognized risk factors. Of note, no differences were detected when separately considering individual ketone body subspecies (3).

During ketoacidosis, mainly occurring in absolute insulin deficiency such as type 1 diabetes, ketone body levels increase substantially because of increased hepatic production (15). In type 2 diabetes, circulating ketone bodies, assessed after an overnight fast, are usually also increased (16,17). In contrast, in young Finnish adults, fasting ketone bodies correlated negatively with HOMA-IR (18). However, in Finnish men, fasting ketone bodies and levels 2 h into an oral glucose tolerance

Table 2—Association of ketone bodies with incident type 2 diabetes in the general population including all participants ($n = 3,307$)

	(Adjusted) hazard ratio [95% CI]	P value
Model 1: crude analysis	1.62 [1.24, 2.10]	<0.001
Model 2: adjusted for age and sex	1.55 [1.19, 2.04]	0.001
Model 3: model 2 + BMI, waist circumference, blood pressure, hsCRP	1.62 [1.21, 2.17]	0.001
Model 4: model 3 + HOMA-IR	1.63 [1.21, 2.19]	0.001
Model 5: model 4 + lipid related biomarkers	1.63 [1.21, 2.20]	0.001
Model 6: model 5 + renal function	1.62 [1.19, 2.19]	0.002

(Adjusted) hazard ratios [95% CI] are represented as doubling in baseline ketone body levels and were obtained utilizing Cox regression analysis. Model 1 is crude analysis; model 2 is adjusted for age and sex; model 3 is adjusted for model 2 + BMI, systolic blood pressure, waist circumference, and hsCRP; model 4 is adjusted for model 3 + HOMA-IR; model 5 is adjusted for model 4 + total cholesterol, HDL cholesterol, and triglycerides; and model 6 is model 5 + eGFR and urinary albumin excretion.
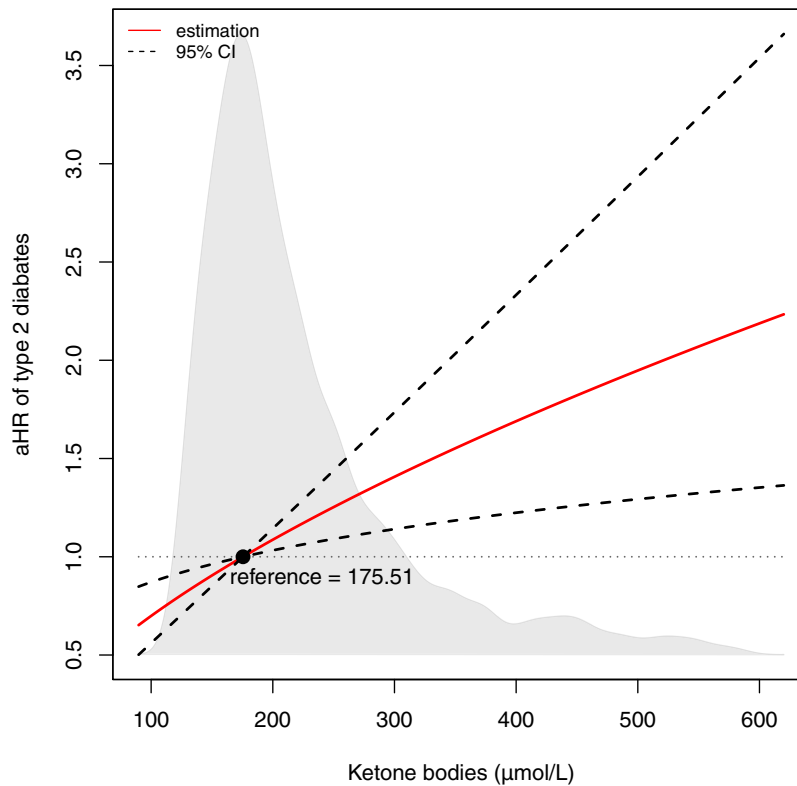
Figure 2—Adjusted hazard ratios (aHR) of type 2 diabetes at different concentrations of ketone bodies. The gray area represents the participant distribution.

test correlated positively with blood glucose (19). Similarly, our study comprising both males and females demonstrated a strong positive association between glucose and circulating ketone bodies. Causality of this association cannot be derived from both studies. However, ketone body infusion into fasted dogs resulted in hypoglycemia (20). Smaller studies in humans indicate a similar effect following ketone ester–containing drinks (21). Thus, increased circulating ketone bodies could represent an early response to maintain normoglycemia in subjects at risk for developing insulin resistance. Further studies are required to specifically address this point. Data on a prospective association of ketone bodies with incident type 2 diabetes are currently scarce and do not allow uniform conclusions. In the aforementioned Finnish study including only male participants ($n = 4,277$), AcAc associated with de novo type 2 diabetes ($P = 0.047$) in a model adjusted for age, BMI, smoking, and physical activity, while, surprisingly, 3HB was not associated with that outcome at all (19). This contrasts with our data demonstrating a firm association of both ketone bodies with incident type 2 diabetes without discernible interaction by sex. When expanding the results in Finnish cohorts to a metabolomics approach including 11,896 young participants, AcAc and 3HB were positively, albeit not significantly, associated with incident type 2 diabetes (22). However, fasting times varied highly, which could conceivably have contributed to offsetting the significance of these findings. A similar reasoning might apply to recent results from the UK Biobank

indicating a potential negative association of 3HB with incident type 2 diabetes, while the outcome was neutral for AcAc (23); this study deliberately used nonfasting conditions. Of note, all three studies measured metabolites on the same NMR platform (Nightingale Health Ltd.) (19,22,23). More research, ideally prospectively using nonfasting and fasting samples from the same participants, would be required to explore these points. Further, the impact of age seems important, since young adults developing insulin-resistant diabetes might differ with respect to metabolic signatures from middle-aged and older participants, when similar follow-up times are applied.

Ketone bodies are the eponymous biomarker of the increasingly popular so-called ketogenic diets that advise followers to consume more than 70% of calories derived from fat (24), which consistently results in high ketone body formation. However, scientific evidence for a superior efficacy of such an approach to prevent type 2 diabetes is low. Although, formally, the design of our study does not allow drawing firm conclusions on the impact of dietary interventions, it adds a cautionary note by demonstrating that high ketone body levels are associated with an opposite outcome than is intended by ketogenic diets. Interestingly, in the Inuit population traditionally following a ketogenic diet, a highly prevalent CPT1A mutation developed, which circumvents ketone body production (25). Such data might indicate that evolutionary chronically increased ketone body levels could be harmful.

Potential limitations of PREVEND are that dietary habits were not recorded, free fatty acids were not determined, and participants are from a relatively homogenous, predominantly White population, preventing conclusions with respect to other ethnicities. In addition, HbA_{1c} levels were not available to establish a diagnosis of type 2 diabetes, and ketone body concentrations were only measured at baseline and not during follow-up. Strengths of our work are the inclusion of a relatively large number of well-characterized subjects, the availability of various biomarkers, and a close and thorough follow-up.

In conclusion, this study demonstrates that fasting ketone bodies strongly and independently associate with incident type 2 diabetes in the general population. Thereby, these data may have important implications for the identification and potential stratification of subjects at risk for developing type 2 diabetes, as well as for considering intervention strategies against the obesity epidemic with its cardiometabolic sequelae.

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