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Retrospective cohort study to examine the association between serum amylase and the incidence of type 2 diabetes mellitus, Toranomon Hospital Health Management Center Study 23 (TOPICS 23)

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ABSTRACT

Introduction Low serum amylase values are cross-sectionally associated with the prevalence of type 2 diabetes mellitus (T2DM) but have not been shown to be longitudinally associated with its incidence. This retrospective cohort (ie, historical cohort) study aimed to examine the association of previously lowered levels of serum amylase with incident T2DM.

Research design and methods Examined were 8316 individuals who had annual health examinations for 6 years (ie, 7 times) at the Toranomon Hospital Health Management Center. The trajectory of serum amylase as the study exposure was classified into two elements: (1) serum amylase level at entry and (2) change in serum amylase, which was expressed as the annual change rate. The annual change rate was calculated by dividing the change in the amylase values according to follow-up periods. Regression analyses were performed to examine the association between low and decreased levels of serum amylase and the incidence of T2DM.

Results Analyzed were 6917 individuals who had not developed T2DM within 1 year after cohort entry. T2DM thereafter occurred in 1021 patients. Cox regression indicated that the adjusted HR (95% CI) for incident T2DM for amylase ≤57 IU/L (quintile (Q) 1) was 0.97 (0.84 to 1.13) compared with amylase ≥58 IU/L (Q2–Q5). Logistic regression indicated that the adjusted OR (95% CI) for an annual change rate of amylase ≤−2.0% (Q1) vs ≥−1.9% (Q2–Q5) was 3.53 (3.00 to 4.16). The adjusted ORs were consistently significant throughout sensitivity analyses according to baseline amylase and the combination of age, body mass index, and hemoglobin A1c.

Conclusions Results showed that not low but previously decreased serum amylase was a risk factor for T2DM, suggesting the significance of periodic examinations of serum amylase values to detect individuals at high risk of T2DM.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Epidemiologically, cross-sectional studies have shown that low serum amylase values are associated with the prevalence of type 2 diabetes mellitus (T2DM).

⇒ Biologically, there is a bidirectional relationship between dysfunctions of pancreatic endocrine and exocrine secretions.

WHAT THIS STUDY ADDS

⇒ Not low serum amylase but reduced serum amylase from previous values was associated with the incidence of T2DM.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings indicate that health examinations should periodically examine serum amylase to identify individuals at high risk of T2DM.

INTRODUCTION

Identifying risk factors in screening for individuals at high risk of diabetes mellitus is essential considering the burden of huge medical costs for treating diabetes, in particular type 2 diabetes mellitus (T2DM), and its complications that seriously impair adult daily life.[1–3]

Serum amylase is one of the most important candidates as a risk factor for T2DM. The rationale for considering that serum amylase is an important candidate as a risk factor for T2DM is the biological finding that there is a bidirectional relationship between dysfunctions of pancreatic endocrine secretion (ie, insulin) and pancreatic exocrine secretions such as for amylase.[4]

There is a cross-sectional association between low serum amylase and the prevalence of T2DM.[5] However, there are little data on whether there is a longitudinal association

between previously lowered amylase levels and T2DM risk. A previous community-based cohort study examined such a longitudinal association but had insufficient statistical power to detect a significant association.[6] Analyzing the trajectory of serum amylase is of value for assessing the ability of serum amylase to predict T2DM risk. Thus, we performed a retrospective cohort (ie, historical cohort) study to examine the possible association of previously lowered levels of serum amylase with the incidence of T2DM.

METHODS

Study participants

The Toranomon Hospital Health Management Center study included a cohort consisting mainly of apparently healthy government employees who underwent a health check-up in Tokyo, Japan. Experimental data from January 1997 to December 2010 were retrospectively examined for 8316 persons who underwent annual health examinations conducted at the Toranomon Hospital Health Management Center for 6 years (ie, taking the exam 7 times).

Definition of study end point and exposure

Study end point was the incidence of T2DM, with information on ascertaining T2DM annually updated. The trajectory of serum amylase as the study exposure was classified into two elements: (1) serum amylase level at entry and (2) change in serum amylase, which was expressed as the annual change rate. The annual change rate was calculated by dividing the change in the amylase values according follow-up periods, which was from study entry until ascertainment of T2DM during the observation period designated as T2DM cases or to the end of this cohort study in non-T2DM controls, that is, those who did not develop T2DM during the study period.

Clinical measurements

Anthropometric measurements, such as of weight and height, were done by trained staff. The body mass index (BMI (kg/m^2)) was calculated. Hospital staff measured blood pressure. Blood samples were collected after an overnight fast (12 hours) and measurements were made using an automated clinical-chemical analyzer (LABOSPECT 008; Hitachi, Tokyo, Japan). Serum amylase, alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), non-high density lipoprotein cholesterol (non-HDL-C), and creatinine were measured by enzymatic methods. Estimated glomerular filtration rate (eGFR) was calculated by the following formula (mL/min/1.73 m^2) using serum creatinine: eGFR creatinine=194×creatinine (mg/dL)$^{-1.094}$×age (years)$^{-0.287}$ (for females, multiplying 0.739). Hemoglobin A1c (HbA1c) was assessed by high-performance liquid chromatography (Tosoh, Tokyo, Japan). Values for HbA1c (%) were estimated as the National Glycohemoglobin Standardization Program (NGSP) equivalent (%) calculated by the equation HbA1c (%)=1.02×HbA1c (Japanese Diabetes Association) (%)+0.25 (%). Diagnoses of T2DM were made according to American Diabetes Association outpatient interview sheets, fasting glucose ≥126 mg/dL, and/or HbA1c 6.5% (NGSP) or higher.[7]

The diagnosis of fatty liver was based on ultrasonographic images, which were stored as photocopies by trained technicians. A gastroenterologist reviewed the photocopies and made the diagnosis of fatty liver. Smoking habits, drinking habits, physical activity (20–30 min of any physical activity at least once a week), and family history of diabetes were assessed by a standard questionnaire.

Statistical analysis

Comparisons between characteristics of the T2DM cases and non-T2DM controls were made using the t-test and the χ^2 test for continuous and categorical variables, respectively. Serum amylase level at entry and the annual change rate in amylase were classified into quintiles from the lowest (Q1) to the highest (Q5). Cox regression analysis was performed to examine the association of the quintiles of amylase at entry with the incidence of T2DM. Logistic regression analysis was performed to examine the relationship between quintiles of the annual change rate of amylase and incident T2DM. To examine T2DM risk for low and decreased amylase values, the quintiles were further divided into two categories (Q1 and Q2–Q5) and the risk of T2DM for Q1 vs Q2–Q5 was determined. In addition, the two categories, which were amylase at entry and annual change rate in amylase, were combined and logistic regression was added to examine the association of the combination with T2DM risk, where Q2–Q5 for both amylase at entry and annual amylase change rate was a referent.

In addition to combining amylase at entry and the annual change rate in amylase, sensitivity analyses were added according to baseline age (median age of the cohort was 49 years and analysis was stratified according to ≤48 and ≥49 years), BMI (≤24.9 or ≥25.0 kg/m^2) and HbA1c (≤5.5% or ≥5.6%) considering that HbA1c of 5.6% is the value at which an 75 g oral glucose tolerance test (OGTT) is recommended in Japan in view of an increased risk of development of diabetes.[8] To maintain the statistically sufficient power to detect a significant risk, data consisting of two categories (ie, Q1 and Q2–Q5) were used as the exposure instead of those consisting of quintiles. Analyses were performed using SPSS (V.19.0, Chicago, Illinois, USA). Statistical significance was considered for $p<0.05$.

RESULTS

Study participants

Excluded were participants who had diabetes at entry or were ascertained to have diabetes the following year which made it impossible to assess changes in the amylase level (n=1121), with serum amylase at entry ≤30 or ≥200 IU/L (n=41),[6] or with missing data on characteristics (n=237).

Table 1 Characteristics of study participants according to the incidence of T2DM

Characteristic	Non-T2DM 5896	T2DM 1021	P value
Age (years)	50±9	50±9	0.888
Male sex (%)	4272 (72.5)	783 (76.7)	0.005
Family history of diabetes (%)	684 (11.6)	390 (38.2)	<0.001
BMI (kg/m^2)	22.7±2.9	23.5±3.3	<0.001
<18.5	315 (5.3)	49 (4.8)	0.473
≥25.0	1134 (19.2)	291 (28.5)	<0.001
Systolic blood pressure (mm Hg)	124±16	124±16	0.121
HbA1c (%)	5.3±0.3	5.5±0.4	<0.001
HbA1c (mmol/mol)	35±4	37±4	<0.001
Fasting plasma glucose (mg/dL)	95±8	100±10	<0.001
Fatty liver (%)	1408 (23.9)	414 (40.5)	<0.001
ALT (IU/L)	24±16	29±31	<0.001
γ-GTP (IU/L)	46±53	56±68	<0.001
Non-HDL-C (mg/dL)	148±33	151±33	0.001
eGFR (mL/min/1.73 m^2)	72±15	77±14	<0.001
Serum amylase level at entry (IU/L)	77±24	73±23	<0.001
Serum amylase level at censor (IU/L)	79±27	71±24	<0.001
Annual change rate of amylase (%)	0.5±3.4	−0.4±9.3	0.002
Current smoking (%)	1097 (18.6)	212 (20.8)	0.104
Current physical activity (%)	2922 (49.6)	476 (46.6)	0.083
Current drinking habit (%)	4685 (79.5)	823 (80.6)	0.401

Data are means±SD or n (%). Differences in the continuous and categorical variables were analyzed by t-test and χ^2 test, respectively.
ALT, alanine aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; GTP, γ-glutamyl transpeptidase; HbA1c, hemoglobin A1c; non-HDL-C, non-high density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus.

After these exclusions, 6917 patients were analyzed, with 1021 incidents of T2DM. Table 1 shows the characteristics of participants with and without incident T2DM. Compared with the non-T2DM controls, patients with T2DM had significantly higher proportions of men, prevalence of family history of diabetes, BMI, prevalence of fatty liver, and abnormalities in non-HDL-C, and eGFR as well as significantly higher HbA1c and fasting plasma glucose values but lower serum amylase values at study entry and a lower annual change rate in amylase.

Figure 1 shows the trajectory of amylase from the beginning of the study to the ascertainment of T2DM in T2DM cases and from the beginning to the end of the cohort study in non-T2DM controls. Serum amylase levels were consistently lower in T2DM cases than in non-T2DM controls throughout the follow-up period. In addition, a trend toward decreases in the amylase level was observed in T2DM cases, although a trend toward elevations was observed in non-T2DM controls.

Serum amylase at study entry and incidence of T2DM

Results of Cox regression analysis showed the association of quintiles of amylase at entry and incident T2DM (table 2A). Age, sex-adjusted HR for T2DM were significantly higher in all risk groups (ie, Q1–Q4) compared with Q5 (model 1: HR (95% CI) for Q5 vs Q1, 1.70 (1.39 to 2.09)). However, significance for the adjusted HR was not observed in any of the four

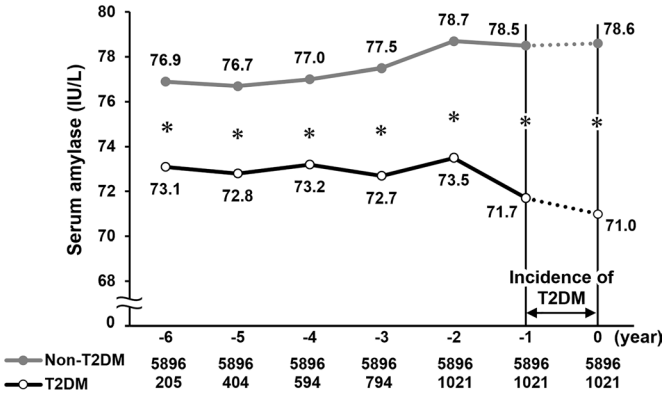

Figure 1 Trajectory of serum amylase (mean±SD) in participants who did and did not have incident type 2 diabetes mellitus (T2DM). Baseline was set at diagnosis of T2DM (in T2DM cases) or at the end of study cohort (in non-T2DM cases). Open circles show incident cases of T2DM and closed circles show non-T2DM cases. *P<0.05.

Table 2 HR or OR for incidence of T2DM according to entry serum amylase level, annual change rate of serum amylase and their combinations

A	N	Event	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Serum amylase at entry					
Q1 (≤57)	1486	270	1.70 (1.39 to 2.09)	1.21 (0.98 to 1.50)	1.07 (0.86 to 1.34)
Q2 (58~67)	1285	190	1.37 (1.10 to 1.70)	1.11 (0.89 to 1.39)	1.05 (0.84 to 1.31)
Q3 (68~78)	1389	203	1.37 (1.10 to 1.69)	1.22 (0.98 to 1.52)	1.15 (0.93 to 1.43)
Q4 (79~94)	1439	213	1.37 (1.11 to 1.69)	1.25 (1.01 to 1.55)	1.19 (0.96 to 1.48)
Q5 (≥95)	1318	145	1.00 (ref)	1.00 (ref)	1.00 (ref)
Male sex			1.19 (1.03 to 1.38)	1.18 (1.00 to 1.39)	1.26 (1.06 to 1.48)
Age			1.01 (1.00 to 1.01)	1.02 (1.02 to 1.03)	1.00 (0.99 to 1.01)
BMI			–	1.05 (1.02 to 1.07)	1.03 (1.01 to 1.06)
SBP			–	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)
eGFR			–	1.03 (1.02 to 1.03)	1.03 (1.02 to 1.03)
Fatty liver			–	1.55 (1.33 to 1.80)	1.35 (1.16 to 1.57)
Current smoking			–	1.03 (0.88 to 1.21)	1.02 (0.87 to 1.19)
Current physical activity			–	0.92 (0.82 to 1.05)	0.97 (0.85 to 1.09)
Current drinking habits			–	1.00 (0.85 to 1.19)	1.11 (0.94 to 1.31)
Family history of diabetes			–	4.44 (3.90 to 5.06)	4.63 (4.06 to 5.27)
HbA1c			–	–	6.49 (5.32 to 7.90)
Q1 (≤57)	1486	270	1.33 (1.15 to 1.53)	1.05 (0.90 to 1.21)	0.97 (0.84 to 1.13)
Q2–Q5 (≥58)	5431	751	1.00 (ref)	1.00 (ref)	1.00 (ref)
B	**N**	**Event**	**Model 4 OR (95% CI)**	**Model 5 OR (95% CI)**	**Model 6 OR (95% CI)**
Annual change rate of serum amylase					
Q1 (≤−2.0)	1459	428	2.14 (1.78 to 2.58)	1.71 (1.40 to 2.08)	1.93 (1.57 to 2.37)
Q2 (−1.9~−0.6)	1357	136	0.54 (0.43 to 0.67)	0.47 (0.37 to 0.60)	0.52 (0.41 to 0.67)
Q3 (−0.5~0.8)	1434	103	0.36 (0.28 to 0.46)	0.33 (0.25 to 0.42)	0.35 (0.27 to 0.45)
Q4 (0.9~2.6)	1347	108	0.39 (0.31 to 0.50)	0.37 (0.29 to 0.47)	0.39 (0.30 to 0.51)
Q5 (≥2.7)	1320	246	1.00 (ref)	1.00 (ref)	1.00 (ref)
Serum amylase at entry			0.99 (0.98 to 0.99)	0.99 (0.99 to 1.00)	0.99 (0.99 to 1.00)
Male sex			1.25 (1.06 to 1.47)	1.27 (1.05 to 1.55)	1.34 (1.10 to 1.64)
Age			1.01 (1.00 to 1.02)	1.03 (1.02 to 1.04)	1.00 (0.99 to 1.01)
BMI			–	1.04 (1.01 to 1.08)	1.02 (0.99 to 1.05)
SBP			–	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)
eGFR			–	1.03 (1.02 to 1.03)	1.03 (1.02 to 1.03)
Fatty liver			–	1.69 (1.41 to 2.02)	1.46 (1.21 to 1.76)
Current smoking			–	1.00 (0.83 to 1.21)	0.97 (0.80 to 1.18)
Current physical activity			–	0.96 (0.82 to 1.11)	0.98 (0.84 to 1.15)
Current drinking habits			–	1.02 (0.83 to 1.24)	1.17 (0.95 to 1.43)
Family history of diabetes			–	5.37 (4.55 to 6.34)	6.15 (5.16 to 7.33)
HbA1c			–	–	9.46 (7.32 to 12.21)
Q1 (≤−2.0)	1459	428	3.89 (3.36 to 4.50)	3.31 (2.83 to 3.88)	3.53 (3.00 to 4.16)
Q2–Q5 (≥−1.9)	5458	593	1.00 (ref)	1.00 (ref)	1.00 (ref)

Continued

Table 2 Continued

C	N	Event	Model 7 OR (95% CI)	Model 8 OR (95% CI)	Model 9 OR (95% CI)
Serum amylase at entry (E) and annual change rate of serum amylase (R)					
E≤57 and R≤−2.0	219	88	6.22 (4.65 to 8.32)	4.23 (3.07 to 5.84)	3.98 (2.85 to 5.55)
E≤57 and R≥−1.9	1267	182	1.54 (1.28 to 1.86)	1.23 (1.01 to 1.51)	1.18 (0.95 to 1.45)
E≥58 and R≤−2.0	1240	340	3.52 (3.00 to 4.14)	3.07 (2.58 to 3.64)	3.37 (2.81 to 4.03)
E≥58 and R≥−1.9	4191	411	1.00 (ref)	1.00 (ref)	1.00 (ref)

Model 1, model 7: adjusted for age, sex.
Model 2, model 8: adjusted for model 1+BMI, SBP, eGFR, fatty liver, current smoking, current physical activity, current drinking habits, family history of diabetes.
Model 3, model 9: adjusted for model 2+HbA1c.
Model 4: adjusted for model 1+serum amylase at entry.
Model 5: adjusted for model 2+serum amylase at entry.
Model 6: adjusted for model 3+serum amylase at entry.
BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; ref, reference; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

categories compared with Q5. In model 3 with full adjustment, the HR (95% CI) for Q1 (amylase ≤57 IU/L) vs Q2–Q5 (amylase ≥58 IU/L) was 0.97 (0.84 to 1.13).

Change rate in amylase and incidence of T2DM

Results of logistic analysis showed the association of quintiles of the annual change in amylase with incident T2DM (table 2B). The OR was slightly lower in intermediate categories (ie, Q2–Q4) compared with Q1. However, the age, sex-adjusted (model 4) and fully adjusted (model 6) ORs (95% CI) for Q1 (≤−2.0%) were 2.14 (1.78 to 2.58) and 1.93 (1.57 to 2.37), respectively. Combining the four categories from Q2 to Q5 (Q2–Q5) as the referent, the fully adjusted OR (95% CI) for Q1 was 3.53 (3.00 to 4.16).

The receiver operating characteristic curve based on the logistic regression model revealed that the area under the curve was 0.78 (95% CI 0.77 to 0.80) (online supplemental figure 1). The best cut-off value for the annual change in amylase, which was determined by the highest Youden Index,[9] was −2.0% at the interval between Q1 and Q2. Using only the cut-off value, the regression model detected only 26% of participants who developed T2DM and 81% of participants who did not develop T2DM. However, using covariates as well as the cut-off value, the regression model could detect 67% of participants who developed T2DM and 75% of participants who did not develop T2DM.

Combination of amylase at entry and change rate of amylase and T2DM risk

Table 2C shows the association of combinations of amylase at entry and change in amylase with the incidence of T2DM. In model 9 with full adjustment for covariates, the OR (95% CI) for low amylase at entry (Q1) and no decreased annual rate of amylase values (Q2–Q5) was 1.18 (0.95 to 1.45). However, the OR for T2DM for a decreased annual rate of amylase values (≤−2.0%) was significant for amylase at entry (OR (95% CI) 3.37 (2.81 to 4.03) for Q2–Q5; 3.98 (2.85 to 5.55) for Q1) compared with Q2–Q5 for the annual amylase change rate and Q2–Q5 for amylase at entry.

Sensitivity analysis

Online supplemental table 1 shows the association of the combination of amylase at entry and the annual amylase change rate with the incidence of T2DM according to baseline age, BMI, and HbA1c. However, the results were similar to the overall analysis as shown in table 2C. Compared with Q2–Q5 for the annual amylase change rate and Q2–Q5 for amylase at entry, the ORs for low amylase at entry (Q1) and no decreased annual rate of amylase values (Q2–Q5) were comparable or slightly higher. However, the ORs for T2DM for a decreased annual rate of amylase values (Q1) were significantly higher throughout the sensitivity analysis.

DISCUSSION

In our study, low serum amylase was not associated with incident T2DM after adjustment for several confounders, although when incident T2DM was adjusted only for age and sex the association was significant. Thus, not low but previously decreased serum amylase was a risk factor for T2DM, suggesting the significance of periodic examinations of serum amylase values for identifying individuals at high risk of T2DM.

The relationship between low levels of serum amylase and T2DM could be explained by classic T2DM risk factors. Actually, the HRs of T2DM for family history of diabetes, HbA1c, and obesity indicators such as BMI and fatty liver were significant (table 2A). In addition, these confounders were found to be associated with serum amylase levels in our cohort (online supplemental table 2).

With regard to obesity, its association with low levels of amylase was previously reported.[10] Serum amylase

may seem to become elevated because the volume of the pancreas increases with obesity.[11] However, obesity-induced hyperinsulinemia paradoxically impairs amylase secretion. When pancreatic acinar cells, which are responsible for exocrine functions, are continuously exposed to high concentrations of insulin, changes in their functions occur. In fact, it was reported that insulin modulates insulin receptors on pancreatic atria in mouse experiments (in vivo) and that elevated insulin secretion and/or severe insulin resistance resulted in downregulation of insulin receptor expression and inhibition of insulin signaling in pancreatic atrial cells.[12] Of note, we need data on serum insulin to support this mechanism, but such data were unfortunately not available.

The second finding was that reduced serum amylase was significantly associated with T2DM risk when adjusted for age and sex and several additional confounders. Furthermore, this finding was consistent, regardless of baseline amylase levels and their combinations with age, BMI, and/or HbA1c, which indicated that the association of decreased amylase with T2DM risk was independent of classic T2DM risk factors. It was reported that the pancreas is atrophic in patients with T2DM compared with healthy individuals.[11 13] A plausible explanation is that the decreased serum amylase reflects decreased pancreas volume leading to declines in insulin secretion and hyperglycemia, even though individuals who develop diabetes are most often obese and their pancreases have been previously enlarged, although those with obesity who do not develop diabetes maintain their pancreatic volume.

The strength of this study is that this is the first cohort study to include a large number of participants to examine whether there is an association of previously lowered levels of serum amylase with the incidence of type 2 diabetes. Several limitations must be mentioned. First, we did not discriminate serum amylase derived from the pancreas from that derived from salivary glands. Although a previous study reported that pancreatic serum amylase secretion was decreased in the presence of hyperglycemia, the actual level of pancreatic amylase in study participants with low total serum amylase is unknown and should be determined.[6] Second, information was not available to distinguish between type 3c (pancreatogenic) diabetes mellitus and T2DM. Testing for exocrine pancreatic insufficiency, imaging studies, and a history of underlying pancreatic diseases were not available. In particular, chronic pancreatitis, one of the underlying diseases of the pancreas, is known to progress to diabetes mellitus and may be a confounding factor in the present results. In addition, although the cut-off for the serum amylase level in this study was ≤30 or ≥200 IU/L, the results did not change even after exclusion of participants who fell outside that range during the follow-up period. Therefore, the possibility of the influence of chronic pancreatitis on the results was considered to be very small. Third, we had no information on abdominal obesity indicators such as waist circumference, visceral fat area, and fatty pancreas that are potentially associated with low serum amylase values.[14–16] Thus, the T2DM risk in relation to amylase could be overestimated. Similarly, we had no demographic data such as on education, marital status, occupation associated with shift work and long working hours, socio-economic status, and amount of alcohol consumption that have been associated with prevalent T2DM.[17–19] Fourth, this cohort included participants who had to be excluded from the analysis because of missing data. Furthermore, there were statistically significant differences in several characteristics between participants that were excluded because of missing data and those included in the analysis, although the incidence of T2DM did not differ (online supplemental table 3). The effect of missing data on study results is likely to be small considering that the proportion of participants excluded from the analysis was small (3.3%=237/7154). In addition, the differences across the two groups were not extremely unbalanced, even if statistically significant. However, a potential selection bias could not be ruled out.

In conclusion, results of this retrospective cohort study suggested that not low serum amylase levels but decreased amylase from previous values is a risk factor for T2DM. The finding urges health examinations to include periodical examinations of serum amylase for identifying individuals at high risk of T2DM. Further studies are needed to elucidate the underlying mechanisms of the finding.

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Contributors II, SK, and HS developed the study design, researched the data, contributed to discussions, wrote the manuscript, and reviewed and edited the manuscript. KF, TO, YT, MH, YMa, YMo, TK, RH, and YA researched the data, contributed to discussions, wrote the manuscript, and reviewed and edited the manuscript. HS planned and supervised this research, developed the study design, researched the data, contributed to discussions, wrote the manuscript, and reviewed and edited the manuscript. II and HS are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was conducted according to the Japanese Government's Ethical Guidelines for Medical and Health Research Involving Human Subjects and in accordance with the Declaration of Helsinki. The ethics committee of the Niigata University faculty of medicine also reviewed the protocol (no. 2015-1628). Participants gave informed consent to participate in the study before taking part.

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REFERENCES

1 American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care* 2018;41:917–28.
2 Rubin RR, Peyrot M. Quality of life and diabetes. *Diabetes Metab Res Rev* 1999;15:205–18.
3 Trikkalinou A, Papazafiropoulou AK, Melidonis A. Type 2 diabetes and quality of life. *World J Diabetes* 2017;8:120–9.
4 Rickels MR, Norris AW, Hull RL. A tale of two pancreases: exocrine pathology and endocrine dysfunction. *Diabetologia* 2020;63:2030–9.
5 Ko J, Cho J, Petrov MS. Low serum amylase, lipase, and trypsin as biomarkers of metabolic disorders: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2020;159:107974.
6 Nakajima K, Nemoto T, Muneyuki T, *et al*. Low serum amylase in association with metabolic syndrome and diabetes: a community-based study. *Cardiovasc Diabetol* 2011;10:34.
7 American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010;33 Suppl 1:S62–9.
8 Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus, Seino Y, Nanjo K, *et al*. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Investig* 2010;1:212–28.
9 Youden WJ. Index for rating diagnostic tests. *Cancer* 1950;3:32–5.
10 Nakajima K. Low serum amylase and obesity, diabetes and metabolic syndrome: a novel interpretation. *World J Diabetes* 2016;7:112–21.
11 Macauley M, Percival K, Thelwall PE, *et al*. Altered volume, morphology and composition of the pancreas in type 2 diabetes. *PLOS ONE* 2015;10:e0126825.
12 Mössner J, Logsdon CD, Goldfine ID, *et al*. Regulation of pancreatic acinar cell insulin receptors by insulin. *Am J Physiol* 1984;247:G155–60.
13 Silva ME, Vezozzo DP, Ursich MJ, *et al*. Ultrasonographic abnormalities of the pancreas in IDDM and NIDDM patients. *Diabetes Care* 1993;16:1296–7.
14 Nakajima K, Oshida H, Muneyuki T, *et al*. Independent association between low serum Amylase and non-alcoholic fatty liver disease in asymptomatic adults: a cross-sectional observational study. *BMJ Open* 2013;3:e002235.
15 Wu WC, Wang CY. Association between non-alcoholic fatty pancreatic disease (NAFPD) and the metabolic syndrome: case-control retrospective study. *Cardiovasc Diabetol* 2013;12:77.
16 Dias JP, Schrack JA, Shardell MD, *et al*. Association of abdominal fat with serum amylase in an older cohort: the Baltimore longitudinal study of aging. *Diabetes Res Clin Pract* 2016;116:212–7.
17 Hwang J, Shon C. Relationship between socioeconomic status and type 2 diabetes: results from Korea national health and nutrition examination survey (KNHANES) 2010-2012. *BMJ Open* 2014;4:e005710.
18 Kivimäki M, Virtanen M, Kawachi I, *et al*. Long working hours, socioeconomic status, and the risk of incident type 2 diabetes: a meta-analysis of published and unpublished data from 222 120 individuals. *Lancet Diabetes Endocrinol* 2015;3:27–34.
19 Howard AA, Arnsten JH, Gourevitch MN. Effect of alcohol consumption on diabetes mellitus: a systematic review. *Ann Intern Med* 2004;140:211–9.