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Original Contribution

Presence of Gallstones or Kidney Stones and Risk of Type 2 Diabetes

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Recent evidence suggests that gallstones and kidney stones are associated with insulin resistance, but the relation between stone diseases and the risk of developing type 2 diabetes mellitus is not clear. Participants in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study (Potsdam, Germany) provided information about the presence of gallstones and kidney stones at recruitment between 1994 and 1998. On biennial questionnaires, participants reported newly diagnosed type 2 diabetes mellitus, and confirmation was obtained from treating physicians. During a mean follow-up period of 7.0 years between 1994 and 2005, 849 incident cases of type 2 diabetes were identified among 25,166 participants. After adjustment for sex, age, waist circumference, and lifestyle risk factors, persons with reported gallstones ($n = 3,293$) had an increased risk of type 2 diabetes (relative risk = 1.42, 95% confidence interval: 1.21, 1.68). Among the 23,817 participants with information on reported kidney stones (784 cases of incident diabetes), those who developed kidney stones ($n = 2,468$) were not at increased risk of diabetes in multivariable-adjusted models (relative risk = 1.05, 95% confidence interval: 0.86, 1.27). These findings suggest that gallstones, but not kidney stones, may predict the risk of developing type 2 diabetes, providing physicians with an interventional opportunity to implement adequate prevention measures.

cohort studies; diabetes mellitus, type 2; gallstones; kidney calculi; insulin resistance; nephrolithiasis; obesity; risk factors

Abbreviations: CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; RR, relative risk.

Gallstones and kidney stones are diseases with high prevalence (1, 2). The increasing incidence of stone diseases over the past several decades (2–4) parallels modifications in dietary habits and physical activity associated with the Western lifestyle (5, 6). Indeed, obesity and the metabolic syndrome have been established as risk factors for kidney stone and gallstone formation (7–10). Moreover, current epidemiologic evidence suggests that persons with diabetes mellitus are at increased risk of stone formation (11–13). On the other hand, gallstones and nephrolithiasis may be associated with increased risk of diabetes. Hepatic insulin resistance was recently shown to directly promote gallstone formation in an animal model (14). Thus, stone formation and diabetes development may share pathophysiologic pathways, but it remains unclear whether the occurrence of gallstones or kidney stones predicts the risk of type 2 diabetes, since prospective data on an independent association are lacking. Therefore, we investigated the relation between gallstones and kidney stones and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam, a large prospective cohort study.

MATERIALS AND METHODS

Study population

The EPIC-Potsdam Study is part of EPIC, a large-scale Europe-wide prospective cohort study, and includes 27,548 persons (16,644 women and 10,904 men). Participants were recruited between 1994 and 1998 from the general population

of Potsdam, Germany, with the preferred ages of 35–65 years in women and 40–65 years in men (15). The baseline examination included standardized blood pressure measurements, anthropometric measurements, self-administered questionnaires on diet and lifestyle, computer-guided interviews that included questions about prevalent diseases, and blood sampling. Informed consent was obtained from all participants, and approval was given by the ethical committee of the state of Brandenburg, Germany. Information on incident diseases and changes in lifestyle is assessed biennially by means of self-administered questionnaires (16).

The presence of diabetes mellitus at baseline was evaluated by a physician using information on self-reported medical diagnoses, medication records, and dieting behavior. Uncertainties regarding a correct diagnosis were clarified with the participant or his/her physician. After exclusion of participants with a history of diabetes at baseline, unconfirmed self-reported diabetes during follow-up, missing follow-up data, or missing confounder information, 25,166 participants remained for analyses. For analyses regarding gallstones, we furthermore excluded 12 participants with missing data on gallstone status, which left 25,154 participants in the analysis cohort. With regard to kidney stones, we excluded 1,349 participants (including 65 with incident type 2 diabetes) with missing data on kidney stone status, leaving 23,817 participants.

For additional analyses including relevant biomarkers for diabetes (glucose, triglycerides, and cholesterol), we used a case-cohort design comprising a random subcohort ($n = 2{,}500$) of the EPIC-Potsdam subjects and all subjects with incident cases of type 2 diabetes who provided blood samples. After applying the same exclusion criteria as presented elsewhere (17) and after further applying the abovementioned exclusion criteria regarding stone status, 722 cases and 2,180 noncases remained for analyses of gallstones and diabetes risk and 665 cases and 2,053 noncases remained for analyses of kidney stones and type 2 diabetes risk.

Ascertainment of type 2 diabetes

Incident cases of diabetes were defined as a self-report of a diabetes diagnosis, use of diabetes-relevant medication, or dietary treatment due to diabetes. All potential incident cases identified during the course of follow-up were verified via questionnaires mailed to the diagnosing physician. The questionnaires asked about the date and type of diagnosis and requested information on diagnostic tests and treatment. Only subjects with a physician's diagnosis of type 2 diabetes (*International Classification of Diseases*, Tenth Revision, code E11) and a diagnosis date after the baseline examination were considered to have a confirmed incident case of type 2 diabetes.

Assessment of exposure and covariates

Information on prevalent diseases, including the prevalence of gallstones and kidney stones, was assessed by trained interviewers during a computer-guided interview. The participants were asked, ''Have you ever been diagnosed with gallstones?'' and ''Have you ever been diagnosed with kidney stones?'' Possible responses included ''yes,'' ''no,'' and ''don't know.'' In addition, lifestyle characteristics, including regular physical exercise (including cycling) and smoking history, were documented at baseline. Physical exercise was defined as the mean amount of time spent in leisure-time physical activities during the summer and winter (hours/week). Anthropometric data and blood pressure were measured by trained and quality-monitored personnel (18). Waist circumference was measured midway between the lower rib margin and the superior anterior iliac spine to the nearest 0.5 cm with a nonstretching tape applied horizontally and with proper use controlled by a mirror (19). Blood pressure was measured in the sitting position on the right arm with the arm elevated at heart level; the average of the second and third readings was used. For the subcohort and all cases with blood samples, plasma levels of glucose, total cholesterol, and triglycerides were measured with the automatic ADVIA 1650 analyzer (Siemens Medical Solutions, Erlangen, Germany).

Statistical analysis

Statistical analysis was performed using SAS software, release 9.1 (SAS Institute Inc., Cary, North Carolina). All tests performed were 2-sided, with $P < 0.05$ considered statistically significant. Baseline characteristics were compared for participants with and without stones using Student's unpaired t test, Wilcoxon's unpaired rank-sum test, or the χ^2 test.

We examined the association of the presence of gallstones or kidney stones with risk of type 2 diabetes by calculating sex-adjusted and multivariable-adjusted relative risks using Cox proportional hazards regression. Age was used as the underlying time variable in the counting process, with entry and exit time being defined as the subject's age at recruitment and age at diabetes diagnosis or censoring, respectively. We stratified by age at recruitment so that results would be less sensitive to violations of the proportional hazards assumption.

The sex-adjusted model was model 1. The multivariable-adjusted models included education (in training or no training, vocational training, technical school, or technical college or university degree), occupational activity (light, moderate, or heavy), sport activity (0, 0.1–4.0, or >4.0 hours/week), cycling (0, 0.1–2.4, 2.5–4.9, or ≥5 hours/week), smoking (never smoker, past smoker, current smoker of <20 cigarettes/day, or current smoker of ≥20 cigarettes/day), and alcohol intake (0, 0.1–5, 5.1–10.0, 10.1–20.0, 20.1–40.0, or >40 g/day) (model 2), and additionally waist circumference (cm; continuous) (model 3). Further, the influence of additional adjustment for body mass index (weight (kg)/height $(m)^2$; continuous) and hypertension was also studied. Abdominal obesity was defined as a waist circumference greater than or equal to 102 cm in men and greater than or equal to 88 cm in women. Prevalent hypertension was defined as systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg or self-reporting of a diagnosis of hypertension or use of antihypertensive medication. Interactions between stone disease and important risk factors were tested using cross-product terms in the fully adjusted models.

Table 1. Baseline Characteristics[a] of Participants According to Gallstone or Kidney Stone Disease Status (n = 25,166), EPIC-Potsdam Study, 1994–1998

Characteristic	Gallstones[b]			Kidney Stones[c]		
	No	Yes	*P* Value	No	Yes	*P* Value
Sociodemographic factors	(n = 21,861)	(n = 3,293)		(n = 21,349)	(n = 2,468)	
Age, years	49.0 (8.9)	53.8 (8.3)	<0.0001	49.2 (8.9)	53.2 (8.4)	<0.0001
Sex, % male	40.5	26.7	<0.0001	36.6	52.3	<0.0001
Body mass index[d]	25.8 (4.1)	27.9 (4.8)	<0.0001	26.0 (4.2)	27.0 (4.3)	<0.0001
Waist circumference, cm						
Men	94.0 (9.9)	98.1 (9.6)	<0.0001	94.3 (9.9)	95.7 (10.0)	<0.0001
Women	79.1 (10.7)	85.9 (12.2)	<0.0001	80.0 (11.1)	82.7 (12.1)	<0.0001
Sport activity, hours/week	1.0 (1.7)	0.8 (1.5)	<0.0001	1.0 (2.9)	0.9 (1.7)	0.015
Cycling, hours/week	1.9 (2.9)	1.7 (2.7)	0.0011	1.8 (2.9)	1.9 (3.1)	0.59
Smoking, %			<0.0001			<0.0001
Never smoker	46.8	53.8		47.8	47.6	
Former smoker	32.1	30.0		31.1	36.2	
Current smoker of <20 cigarettes/day	15.2	12.3		15.3	11.6	
Current smoker of ≥20 cigarettes/day	6.0	3.9		5.9	4.6	
Educational achievement, %			<0.0001			0.202
No vocational training	2.8	5.3		3.2	3.7	
Vocational training	34.2	37.9		34.9	33.1	
Technical school	24.3	28.8		24.8	25.0	
Technical college or university	38.6	28.0		37.1	38.2	
Occupational activity, %			0.0004			0.081
Light	59.8	60.3		59.8	60.2	
Moderate	33.0	34.3		33.4	32.0	
Heavy	7.2	5.3		6.8	7.8	
Alcohol intake, g/day	14.5 (19.0)	10.3 (14.3)	<0.0001	13.8 (18.5)	13.9 (17.2)	0.88
Hypertension, %	45.7	55.5	<0.0001	45.9	61.1	<0.0001
Biomarkers[e], mg/dL	(n = 1,961)	(n = 286)		(n = 1,893)	(n = 223)	
Glucose	87.8 (14.5)	90.9 (14.0)	0.016	88.1 (14.4)	88.2 (14.7)	0.85
Triglycerides	111.2 (78.6)	129.6 (93.3)	0.0017	111.7 (77.4)	124.4 (96.1)	0.057
Total cholesterol	174.4 (35.3)	181.5 (35.5)	0.0016	174.1 (34.9)	181.6 (38.2)	0.003

Abbreviation: EPIC, European Prospective Investigation into Cancer and Nutrition.

[a] Baseline characteristics of participants are expressed as mean values (with standard deviations in parentheses) or percentages and were compared for participants with and without stones using Student's unpaired t test or the χ^2 test.

[b] From the entire cohort, 12 participants with unknown or missing data on gallstone status were excluded.

[c] From the entire cohort, 1,349 participants (including 65 cases of incident type 2 diabetes) with unknown or missing data on kidney stone status were excluded.

[d] Weight (kg)/height (m)^2.

[e] Based on a randomized subcohort of the EPIC-Potsdam Study.

In addition, we performed analyses including glucose, triglycerides, and total cholesterol in the case-cohort sample. Relative risks were calculated as hazard ratios for type 2 diabetes according to the presence of gallstones or kidney stones using a weighted Cox proportional hazards model, modified for the case-cohort design according to the Prentice method (20).

RESULTS

Of the 27,548 persons in the entire EPIC-Potsdam cohort, 25,154 were included in the analyses of gallstones and 23,817 in the analyses of kidney stones. Among these persons, 3,293 participants reported gallstones, while 2,468 reported kidney stones. During a mean follow-up period of

Table 2. Relative Risk of Type 2 Diabetes According to the Presence of Gallstones or Kidney Stones ($n = 25,166$), EPIC-Potsdam Study, 1994–2005

	Gallstones						Kidney Stones					
	No[a]		Yes				No[a]		Yes			
	No.	%	No.	%	RR	95% CI	No.	%	No.	%	RR	95% CI
Cases	631	2.9	218	6.6			659	3.1	125	5.1		
Person-years	153,663		23,023				147,878		17,063			
Relative risk												
Sex-adjusted model (model 1)					2.03	1.73, 2.38					1.19	0.98, 1.45
Multivariable-adjusted models												
Model 2[b]					1.95	1.66, 2.29					1.20	0.99, 1.46
Model 3 (model 2 + waist circumference)[c]					1.42	1.21, 1.68					1.05	0.86, 1.27

Abbreviations: CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; RR, relative risk.

[a] Referent (relative risk = 1).

[b] Adjusted for age, sex, education (in training or no training, vocational training, technical school, or technical college or university degree), occupational activity (light, moderate, or heavy), sport activity (0, 0.1–4.0, or >4.0 hours/week), cycling (0, 0.1–2.4, 2.5–4.9, or ≥5 hours/week), smoking (never smoker, past smoker, current smoker of <20 cigarettes/day, or current smoker of ≥20 cigarettes/day), and alcohol intake (0, 0.1–5, 5.1–10.0, 10.1–20.0, 20.1–40.0, or >40 g/day).

[c] Further adjustment for body mass index and hypertension did not influence the risk estimates.

7.0 years (standard deviation, 1.9) between 1994 and 2005, 849 subjects developed incident type 2 diabetes mellitus.

Persons with reported stone disease, regardless of whether these were gallstones or kidney stones at baseline, were older, had a higher body mass index and waist circumference, were less likely to be smokers, and more often had a history of hypertension than persons without stones (Table 1). The presence of gallstones (but not kidney stones) was related to educational achievement and occupational activity. After adjustment for sex and age, gallstones were related to educational achievement but were no longer related to occupational activity. After additional adjustment for waist circumference, the association between education and gallstones lost significance. Persons with gallstones were more likely to be women, whereas kidney stones more often occurred among men. Consequently, 91.0% of men were free of gallstones, whereas 85.6% were free of kidney stones at baseline. In contrast, 84.3% of women reported no gallstones and 92.0% no kidney stones.

Table 2 depicts the estimated relative risks of type 2 diabetes according to the presence of gallstones and kidney stones. After adjustment for age, sex, smoking status, alcohol consumption, education, and physical activity (model 2), persons with gallstones had a significantly increased risk of type 2 diabetes (relative risk (RR) = 1.95, 95% confidence interval (CI): 1.66, 2.29). The observed association was attenuated after further adjustment for waist circumference (model 3), but it remained statistically significant. Further adjustment for body mass index and hypertension did not influence the risk estimate (RR = 1.43, 95% CI: 1.21, 1.68). In model 2, we observed a borderline-significant association between kidney stones and risk of type 2 diabetes (RR = 1.20, 95% CI: 0.99, 1.46). This association was completely abolished after adjustment for waist circumference (model 3; RR = 1.05, 95% CI: 0.86, 1.27) and was not further influenced by additional adjustment for body mass index and hypertension (RR = 1.04, 95% CI: 0.85, 1.26).

We investigated whether there was an interaction between the presence of gallstones or kidney stones and sex, anthropometric measures, or hypertension. Significant interactions with gallstones were observed for waist circumference (continuous; $P = 0.0015$) and body mass index (continuous; $P = 0.003$) in multivariable-adjusted models. Among anthropometric measures, waist circumference as a measure of abdominal obesity was the most important predictor of diabetes risk in our study. The association between gallstones and risk of type 2 diabetes was slightly weaker among participants with abdominal obesity (RR = 1.37, 95% CI: 1.13, 1.66) than in those without it (RR = 1.48, 95% CI: 1.11, 1.97) (Table 3, model 3). Although the test for interaction between the presence of gallstones and menopausal status failed significance in the multivariable-adjusted model including waist circumference ($P = 0.14$), the risk estimates in the fully adjusted model seemed to differ by menopausal status (Table 3). However, these subanalyses were hampered by low numbers of cases among premenopausal women.

To determine whether the associations between stone diseases and risk of type 2 diabetes could be explained by selected biomarkers, we performed a subanalysis in a case-cohort study. In the sex-adjusted model (model 1), the risk of type 2 diabetes increased approximately 2-fold among persons with reported gallstones (RR = 2.08, 95% CI: 1.67, 2.59), confirming the data in the full cohort. After adjustment for age, sex, smoking status, alcohol consumption, education, physical activity, and waist circumference (model 3), persons with gallstones had a relative risk of 1.54 (95% CI: 1.19, 1.99). Further adjustment for glucose, total cholesterol, and triglycerides did not substantially affect the risk estimates (RR = 1.51, 95% CI: 1.17, 1.96) (Figure 1). With respect to kidney stones, further adjustment for

Table 3. Relative Risk of Type 2 Diabetes According to the Presence of Gallstones for Specific Subgroups ($n = 25,166$), EPIC-Potsdam Study, 1994–2005

	No Gallstones[a]		Gallstones			
	No.	%	No.	%	Relative Risk	95% Confidence Interval
Abdominal obesity status[b]						
No abdominal obesity						
Cases	258	1.5	60	3.0		
Person-years	124,925		14,689			
Relative risk						
Model 1 (sex-adjusted model)					1.70	1.28, 2.27
Multivariable-adjusted models						
Model 2[c]					1.67	1.25, 2.23
Model 3 (model 2 + waist circumference)					1.48	1.11, 1.97
Abdominal obesity						
Cases	373	8.7	158	12.6		
Person-years	28,738		8,334			
Relative risk						
Model 1 (sex-adjusted model)					1.53	1.26, 1.86
Multivariable-adjusted models						
Model 2[c]					1.48	1.22, 1.79
Model 3 (model 2 + waist circumference)					1.37	1.13, 1.66
Menopausal status (women only)						
Premenopausal						
Cases	51	0.8	12	1.9		
Person-years	45,611		4,371			
Relative risk						
Model 1 (sex-adjusted model)					2.04	1.08, 3.86
Multivariable-adjusted models						
Model 2[c]					1.81	0.95, 3.45
Model 3 (model 2 + waist circumference)					0.83	0.40, 1.73
Postmenopausal						
Cases	100	2.9	78	7.1		
Person-years	24,028		7,575			
Relative risk						
Model 1 (sex-adjusted model)					2.34	1.74, 3.16
Multivariable-adjusted models						
Model 2[c]					2.26	1.67, 3.06
Model 3 (model 2 + waist circumference)					1.70	1.25, 2.31

Abbreviation: EPIC, European Prospective Investigation into Cancer and Nutrition.

[a] Referent (relative risk = 1).

[b] Abdominal obesity was defined as waist circumference ≥102 cm in men and ≥88 cm in women.

[c] Adjusted for age, sex, education (in training or no training, vocational training, technical school, or technical college or university degree), occupational activity (light, moderate, or heavy), sport activity (0, 0.1–4.0, or >4.0 hours/week), cycling (0, 0.1–2.4, 2.5–4.9, or ≥5 hours/week), smoking (never smoker, past smoker, current smoker of <20 cigarettes/day, or current smoker of ≥20 cigarettes/day), and alcohol intake (0, 0.1–5, 5.1–10.0, 10.1–20.0, 20.1–40.0, or >40 g/day).

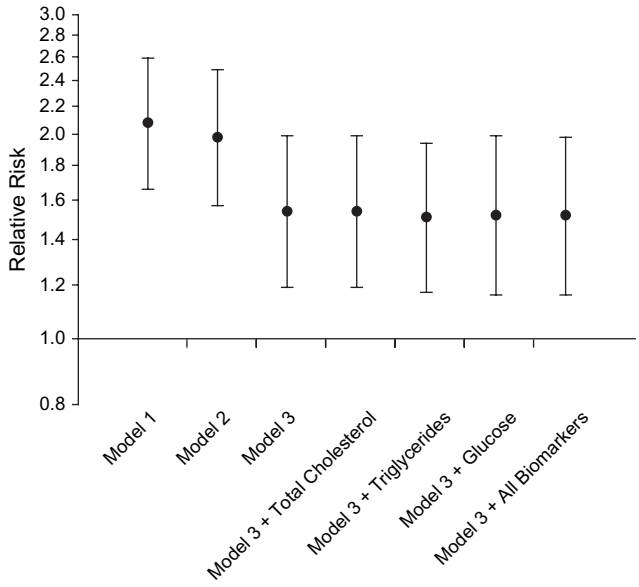

Figure 1. Relative risk of type 2 diabetes according to the presence of gallstones, based on a case-cohort study of members of the EPIC-Potsdam cohort ($n = 2{,}902$), 1994–2005. The sex-adjusted model was model 1. Results from model 2 were adjusted for age, sex, education (in training or no training, vocational training, technical school, or technical college or university degree), occupational activity (light, moderate, or heavy), sport activity (0, 0.1–4.0, or >4.0 hours/week), cycling (0, 0.1–2.4, 2.5–4.9, or ≥5 hours/week), smoking (never smoker, past smoker, current smoker of <20 cigarettes/day, or current smoker of ≥20 cigarettes/day), and alcohol intake (0, 0.1–5, 5.1–10.0, 10.1–20.0, 20.1–40.0, or >40 g/day). Model 3 results were adjusted for all of the factors in model 2 plus waist circumference. Bars, 95% confidence interval. (EPIC, European Prospective Investigation into Cancer and Nutrition).

biomarkers did not change the results considerably (data not shown).

DISCUSSION

To our knowledge, the present study provides the first prospective data on the relation between gallstones and kidney stones and risk of type 2 diabetes mellitus. The findings indicate that persons who develop stones are at increased risk of type 2 diabetes. The occurrence of gallstones appears to predict diabetes independently of obesity, hypertension, glucose, triglycerides, total cholesterol, and established lifestyle risk factors for diabetes. In persons with kidney stones, the increased risk of diabetes seems to be largely attributable to anthropometric measures. Thus, in contrast to gallstones, kidney stones alone may not be associated with risk of type 2 diabetes independently of established risk factors.

As previously described (21), the prevalence of gallstones was higher in women than in men, and, on the contrary, the prevalence of kidney stones was higher in men than in women. With respect to gallstones, female sex hormones are most likely to be responsible for the higher prevalence in women (22). The higher prevalence of kidney stones in men may be due to differences in the intake of animal protein (23) and the prevalence of certain comorbid conditions, particularly hypertension (24). Interestingly, we observed that the presence of gallstones (but not kidney stones) was related to educational attainment. This relation may be explained by the fact that low education is associated with obesity (25). However, the factors linking socioeconomic or educational status with gallstone formation have not been sufficiently studied as yet.

The underlying mechanisms linking diabetes and gallstone disease remain to be elucidated. Recently, Biddinger et al. (14) demonstrated in mice that insulin resistance may directly promote the formation of gallstones. In their study, increased biliary cholesterol secretion and the production of a lithogenic bile salt profile were established as potential mechanisms linking hepatic insulin resistance and gallstone formation. Against the background of these novel experimental data, our findings suggest that similar mechanisms may be relevant in humans. In line with this notion, an increased risk of gallstone formation has been reported in persons with hyperinsulinemia, even before manifest diabetes has developed (26).

In our study, we observed a rather weak and nonsignificant association of nephrolithiasis with type 2 diabetes. It is notable, however, that this association was no longer evident after adjustment for abdominal obesity, and thus kidney stones did not independently predict diabetes risk. However, we cannot rule out the possibility that specific types of stones, particularly uric acid stones, are associated with risk of type 2 diabetes. Higher proportions of persons with diabetes were reported among persons developing uric acid stones than among persons developing calcium stones (27). This has been explained by a decrease in urine pH due to insulin resistance and obesity (13, 28). Nonetheless, it remains to be elucidated whether the occurrence of uric acid stones is independently associated with diabetes risk.

Among the strengths of our investigation are the prospective study design and the comprehensive data on numerous covariates, including anthropometric factors, blood pressure, and biomarkers (for a subcohort of the EPIC-Potsdam Study). Nevertheless, some limitations of our study should be discussed. First, incident and prevalent diabetes cases in our study were based on self-reports verified through the treating physician. Thus, a certain proportion of total diabetes may not have been identified. If, however, the association between gallstones and unidentified diabetes is similar to that for identified diabetes, our relative risks should be accurate (29). In our subanalysis including biomarkers, we excluded participants with plasma glucose values that fell within the diabetic range at baseline, diminishing the threat of misclassifying undiagnosed diabetes. The risk estimates in this subanalysis were quite similar to those of the analysis carried out in the whole cohort, confirming the robustness of our findings. Second, the assessment of risk factors, including the presence of stones, was based on self-reporting, which is a potential source of bias. However, the relatively high socioeconomic status of our study population may be associated with a sufficient quality of self-reports (30), and the threat of overestimation of exposure may not have been substantial (31). Third, sufficient data on the types of kidney stones, particularly uric acid stones, were not available, so that subgroup analysis of associations of specific stone types

with diabetes could not be conducted. Fourth, our study population was confined to German participants aged 35–65 years at baseline. Therefore, the findings of our study may be specific for a middle-aged Western population, and applicability to older age groups is unclear.

This large prospective cohort study suggests that gallstones may predict the risk of type 2 diabetes. The occurrence of gallstones should be recognized as a risk factor or risk marker for diabetes and may be seen as an occasion to implement adequate lifestyle modifications/prevention measures. The diagnosis of gallstone disease is straightforward and facilitates the communication of an increased diabetes risk to the affected person. Our data support further research into the role of insulin resistance in the pathogenesis of gallstone disease.

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