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.

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...
Assessment of exposure and covariates

Ascertainment of type 2 diabetes

Risk of diabetes mellitus at baseline was evaluated by a physician using information on self-reported medical diagnoses, medication records, and diet and lifestyle. 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 was assessed biennially by means of self-administered questionnaires.

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

<table>
<thead>
<tr>
<th></th>
<th>Gallstones</th>
<th>Kidney Stones</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No*</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Cases</td>
<td>631</td>
<td>2.9</td>
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<tr>
<td>Person-years</td>
<td>153,663</td>
<td>23,023</td>
</tr>
<tr>
<td>Relative risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex-adjusted model (model 1)</td>
<td>2.03</td>
<td>1.73, 2.38</td>
</tr>
<tr>
<td>Multivariable-adjusted models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>1.95</td>
<td>1.66, 2.29</td>
</tr>
<tr>
<td>Model 3 (model 2 + waist circumference)</td>
<td>1.42</td>
<td>1.21, 1.68</td>
</tr>
</tbody>
</table>

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

* Referent (relative risk = 1).

† 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 <10 cigarettes/day, or current smoker of ≥10 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).

‡ Further adjustment for body mass index and hypertension did not influence the risk estimates.
<table>
<thead>
<tr>
<th>Abdominal obesity status</th>
<th>No abdominal obesity</th>
<th>Abdominal obesity</th>
<th>Menopausal status (women only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>258</td>
<td>373</td>
<td>51</td>
</tr>
<tr>
<td>Person-years</td>
<td>124,925</td>
<td>28,738</td>
<td>45,611</td>
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<tr>
<td>Relative risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.70</td>
<td>1.53</td>
<td>2.04</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1.28</td>
<td>1.26</td>
<td>1.08</td>
</tr>
<tr>
<td>models</td>
<td>2.27</td>
<td>1.86</td>
<td>3.86</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.67</td>
<td>1.48</td>
<td>1.81</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1.25</td>
<td>1.22</td>
<td>0.95</td>
</tr>
<tr>
<td>models</td>
<td>2.23</td>
<td>1.79</td>
<td>3.45</td>
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<tr>
<td>Model 3</td>
<td>1.48</td>
<td>1.37</td>
<td>0.83</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1.11</td>
<td>1.13</td>
<td>0.40</td>
</tr>
<tr>
<td>models</td>
<td>1.97</td>
<td>1.66</td>
<td>1.73</td>
</tr>
</tbody>
</table>

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).
bimarkers 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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Drs. Cornelia Weikert and Steffen Weikert contributed equally to this article.

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