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ORIGINAL ARTICLE

Attribution of diabetes to the development of severe liver disease in the general population

Miika Vuorinen[1] | Ville T. Männistö[1] | Veikko Salomaa[2] | Annie Britton[3] | Antti Jula[2] | Satu Männistö[2] | Annamari Lundqvist[2] | Markus Perola[2] | Fredrik Åberg[4]

[1]Departments of Medicine, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland

[2]Finnish Institute for Health and Welfare, Helsinki, Finland

[3]Institute of Epidemiology and Health Care, University College London, London, UK

[4]Transplantation and Liver Surgery Clinic, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

Correspondence
Miika Vuorinen, Gastroenterology and Endoscopy Unit, Kuopio University Hospital, Puijonlaaksontie 2, 70210 Kuopio, Finland.
Email: miika.vuorinen@kuh.fi

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Abstract

Background and Aims: Diabetes is associated with advanced liver disease and predicts mortality regardless of the primary aetiology of the liver disease. Even a family history of diabetes has been linked to advanced liver fibrosis in non-alcoholic fatty liver disease (NAFLD). However, the fraction of liver-related outcomes in the general population that are attributable to diabetes remains unclear.

Methods: The population attributable fraction (PAF) of diabetes for liver disease as a time-dependent exposure was estimated in the Finnish FINRISK study (n = 28 787) and the British Whitehall II study (n = 7855). We also assessed the predictive ability of a family history of diabetes for liver-related outcomes. Incident diabetes data were from drug purchase/reimbursement and healthcare registries (FINRISK) or follow-up examinations (Whitehall II). Incident severe liver outcomes were identified through linkage with national healthcare registries.

Results: Diabetes was associated with a two-fold risk of liver-related outcomes in both the FINRISK (HR, 1.92; $p < .001$) and Whitehall II (HR, 2.37; $p < .001$) cohorts, and this remained significant after adjusting for multiple confounders. PAF analyses demonstrated that diabetes explained 12–14% of the risk for severe liver-related outcomes after 10 and 20 years of follow-up. Also, maternal diabetes increased the risk of liver-related outcomes in the FINRISK (HR, 1.43; $p = .044$) and Whitehall II (HR, 2.04; $p = .051$) cohorts.

Conclusion: Approximately 12%–14% of severe liver-related outcomes are attributable to diabetes at the population level. The association between maternal diabetes and liver disease might suggest a mitochondrial genetic mechanism.

KEYWORDS
cirrhosis, hepatology, hyperglycaemia

Abbreviations: BMI, body mass index; HCC, hepatocellular carcinoma; HCV, hepatitis C; HR, hazard ratio; ICD, International Classification of Diseases; IQR, interquartile range; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PAF, population attributable fraction; PBC, primary biliary cholangitis.

1 | INTRODUCTION

The incidences of liver cirrhosis and hepatocellular carcinoma (HCC) are increasing, and liver cirrhosis imposes a substantial and growing global health burden.[1] Alcohol-related liver disease and non-alcoholic fatty liver disease (NAFLD) are the major causes of advanced liver disease in Western countries, and their role is predicted to increase in developing countries also as hepatitis C (HCV) eradication progresses.[2]

Diabetes is strongly associated with NAFLD,[3,4] advanced liver fibrosis and HCC in the general population.[5,6] Among various metabolic risk factors, diabetes seems to be the most strongly associated with advanced liver disease in NAFLD.[7] Interestingly, even a family history of diabetes has been linked to increased risk of non-alcoholic steatohepatitis (NASH) and liver fibrosis in NAFLD.[8] Furthermore, diabetes has shown to be a marker of poorer prognosis in liver diseases of various causes, such as primary biliary cholangitis (PBC) and HCV,[9,10] and diabetes predicts mortality regardless of the primary aetiology of liver disease.[11] Diabetes also predicted severe liver-related outcomes among alcohol risk drinkers and obese individuals in the general population.[12,13] However, it remains unclear what fraction of liver-related outcomes in the general population is attributable to diabetes.

Population attributable fraction (PAF) analysis is a method of assessing the public health impact of exposures in cohorts.[14] We applied the PAF method in two population-based cohorts, the Finnish FINRISK and the British Whitehall II, with prospective follow-up to estimate the fraction of advanced liver disease in the general population that can be attributed to diabetes as a time-dependent exposure. We also estimated the population-level relevance of a family history of diabetes for liver-related outcomes.

KEYPOINTS

- Diabetes associates with advanced liver disease and predicts mortality regardless of the primary aetiology of the liver disease.
- Our study suggests that approximately 12%–14% of severe liver-related outcomes are attributable to diabetes.
- This elucidates the importance of diabetes in the course of chronic liver diseases but also emphasizes the significant role of other risk factors, which calls for a holistic approach when assessing an individual's risk for future severe liver disease.

2 | MATERIALS AND METHODS

2.1 | Cohorts

2.1.1 | FINRISK

Data were from the Finnish health examination surveys FINRISK 1997, 2002, 2007 and 2012. The FINRISK studies are systematic and standardized cross-sectional population-based health examination surveys carried out in Finland every 5 years since 1972 by the Finnish Institute for Health and Welfare. These studies aim to assess the risk factors for chronic diseases in representative population samples of adults aged 25–74 years who are drawn from the Finnish Population Information System, stratified by sex, 10-year age groups and five to six geographic areas of Finland. The number of invitees has varied over the years, from 7927 to 13 498, and the participation rates have varied from 65% to 76%.[15]

Data were collected from each participant at baseline via interviews, questionnaires and health examination including measures and blood samples using standardized procedures from the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) and European Health Risk Monitoring projects.[16] Blood samples were collected at baseline for a broad spectrum of laboratory measurements and handled using a standardized protocol. Detailed descriptions of the study protocols have been published previously.[15]

The studies were approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District and conducted according to the Declaration of Helsinki. Previously, the studies were approved by the institutional review board of the National Public Health Institute. The FINRISK sample collections were transferred to THL Biobank in 2015 after approval by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District. All subjects provided informed consent for the study and for future registry linkage.

FINRISK data were linked with the Finnish Causes of Death Registry, the Care Register for Health Care (HILMO) for hospitalizations, the Finnish Cancer Registry for malignancies and the Social Insurance Institution of Finland (KELA) registry for drug purchases and drug reimbursements. Data collection in these registries is mandated by law, and the coverage and general quality are consistent and complete.[17] Linkage was performed using the unique personal identity code assigned to all Finnish residents. Follow-up for deaths, hospitalizations, cancers and incident diabetes extended to December 2015.

After the exclusion of subjects with baseline liver disease (ICD-10 codes K70–K77; n = 210) or chronic viral hepatitis (ICD-10 code B18; n = 56), the FINRISK cohort comprised 28 787 subjects.

Diabetes diagnoses were obtained from the Finnish Causes of Death Registry, the Care Register for Health Care (HILMO) and the Social Insurance Institution of Finland (KELA) registry and at baseline also by questionnaires (regarding taking diabetic medication or having a prior known diabetes diagnosis). In addition, an oral glucose tolerance test and glycated haemoglobin were measured in the FINRISK 2002 and 2007 (DILGOM substudy) cohorts. Diabetes medications are reimbursed in Finland, and the Social Insurance Institution of Finland has complete data on entitlements to such reimbursement as well as all prescriptions of diabetes medications. Entitlement to reimbursement

of diabetes medications is based on standard diagnostic criteria for diabetes.[18] Alcohol use, smoking and family history of diabetes were assessed through questionnaires at baseline. Respondents were asked to report how often they consumed alcoholic beverages during the previous year and the average amount (in standard drinks) they consumed per week during the previous month. Average alcohol intake (ethanol grams per day) was calculated based on these data (e.g. one bottle of 330 ml 4.7 alcohol per cent beer = standard drink = 12 g of ethanol). Smoking status was categorized as never smokers, previous smokers and current smokers.

2.1.2 | Whitehall II

The Whitehall II study is an ongoing cohort study of UK civil servants. A total of 10 308 adults (6895 men and 3413 women, aged 35–55) were originally recruited during 1985–1988 from London-based offices. Follow-up clinical examinations have taken place every 4–5 years since that time, with each wave taking 2 years to complete.[19] Participants were linked electronically to National Health Service (NHS) maintained hospitalization, cancer and mortality registers up to December 2019.[20] Because the hospitalization register achieved a high level of national coverage from January 1997 onwards, we set the start of follow-up for liver-related outcomes (study baseline) at the Whitehall II study's fifth follow-up examination (phase 5), which was undertaken in 1997–1999. After exclusion of subjects with missing follow-up data, baseline liver disease or chronic viral hepatitis (n = 15), the Whitehall II study cohort comprised 7855 subjects.

Diagnosis of diabetes was ascertained by questionnaire in phases 1 (1985–1988), 2 (1989), 3 (1992–1993), 4 (1995) and 5 (1997–1999), and glucose tolerance tests in phases 3 and 5, as well as linkage with healthcare registries. Diabetes was defined by at least one of the following criteria: fasting glucose ≥ 7.0 mmol/L (126 mg/dl), use of diabetes medication, reported physician-diagnosed diabetes or registry record of diabetes.

Alcohol use, smoking and family history of diabetes were assessed through questionnaires at baseline and subsequent study phases. Participants were asked to report the number of alcoholic drinks they had consumed in the last 7 days. A standard measure of spirits and a glass of wine were considered to contain 8 g of ethanol, whereas a pint of beer was considered to contain 16 g of ethanol. Participants were also asked to estimate the frequency of their drinking during the last 12 months.

The Whitehall II study was approved by the London-Harrow Research Ethics Committee and the Scotland Research Ethics Committee. All participants who had clinical examinations were asked to give written informed consent.

2.2 | Outcomes

Study endpoints were fatal and non-fatal liver disease (requiring hospital admission or causing HCC or liver-related death) as defined by the ICD-10 codes shown in Table Table S1, in line with a recent consensus paper.[21] We also assessed liver diagnoses related or unrelated to alcohol and HCC as separate outcomes (only in FINRISK).

2.3 | Statistical analyses

For comparing groups, we used chi-square or Mann–Whitney tests as appropriate. Diabetes was considered as a time-dependent exposure variable in Cox regression models to account for both baseline and incident diabetes. These Cox regression models considered an incident liver disease as the outcome and were adjusted for either age and sex or age, sex, BMI (kg/m^2), alcohol use (ethanol grams per week) and smoking status (current, former and never). These covariates were chosen a priori based on clinical relevance. PAF of diabetes, obesity and alcohol risk use for liver outcomes was estimated based on these Cox regression models by using the AF package in R.

Subgroup analyses were performed by baseline BMI (cut-off at 25 kg/m^2) and alcohol use (cut-off at 210 g/week for men and 140 g/week for women). Family history of diabetes was considered in separate Cox regression models adjusted for the same covariates as above. R's cox.zph function was used to test whether the proportional assumption criteria were fulfilled in the models. Data were analysed with R software version 3.6.1 by using the packages survival, rms, tableone and AF.

3 | RESULTS

The total cohort consisted of 28 787 individuals (13 752 men and 15 035 women, mean age 49.5 ±13.7 and BMI 26.9 ±4.8 kg/m^2) from the FINRISK cohort and 7855 individuals (5468 men and 2387 women, mean age 54.7 ±6.1 and BMI 26.0 ±4.0 kg/m^2) from the Whitehall II cohort. Population characteristics are presented in Table 1.

The FINRISK cohort was on average younger and with a higher proportion of females compared with the Whitehall II cohort (50 years vs. 55 years and 52% vs. 30% respectively). In addition, baseline alcohol use was lower in the FINRISK cohort (median [IQR] 30.6 g/week [5.5–94.5] vs. 80 g/week [30.0–160.0]). The prevalence of smoking was two-fold higher in FINRISK compared with Whitehall II (22.8% vs. 11.1%). At baseline, 2203 (7.6%) of individuals in FINRISK and 307 (3.9%) of individuals in Whitehall II had diabetes. During the follow-up and before any liver events, 1822 (6.3%) and 817 (10.4%) new diabetes cases were diagnosed in the FINRISK and Whitehall II cohorts respectively. Parent's and sibling's diabetes seemed to be more common in FINRISK compared with Whitehall II, but some missing information in the Whitehall II data considering relatives' diabetes status might have influenced our interpretation.

Mean follow-up time was 10.7 years (median 12.8 years, IQR 7.8–15.1; range 0.02–17.9 years; 307 022 person-years) in the FINRISK cohort and 21.2 years (median 22.8 years, IQR 0; range 0.5–22.8 years; 166 761 person-years) in the Whitehall II cohort.

TABLE 1 Population characteristics of the FINRISK and Whitehall II cohorts

	FINRISK	Whitehall II
Subjects, n	28 787	7855
Sex male/female, n (%)	13 752/15 035 (52.2)	5468/2387 (30.4)
Age at baseline, years	49.5 ± 13.7	54.7 ± 6.1
Follow-up time, years (IQR)	10.7 (7.8–15.1)	21.2 (0)
Incident liver events, n	194	94
Baseline characteristics		
BMI, kg/m^2	26.9 ± 4.8	26.0 ± 4.0
Alcohol use, g/week	30.6 (5.5–94.5)	80 (30.0–160.0)
Current smoker, n (%)	6478 (22.8)	1086 (11.1)
Diabetes		
Baseline, n (%)	2203 (7.6)	307 (3.9)
Incident cases, n (%)	1822 (6.3)	817 (10.4)
Mother had diabetes, n (%)	4167 (15.4)	566 (9.3)
Father had diabetes, n (%)	2684 (10.1)	483 (8.2)
Parent had diabetes, n (%)[a]	6032 (23.5)	1191 (15.8)
Parent had diabetes, n (%)[a]		
No	19 586 (76.5)	4851 (84.1)
Either mother or father	5556 (21.7)	848 (14.7)
Both	476 (1.9)	67 (1.2)
Sibling had diabetes, n (%)	2552 (10.2)	629 (9.8)

Note: Numbers are mean ± SD unless otherwise reported. Alcohol use is reported as median (IQR).
aCalculated only for those subjects where both mother and father diabetes family history was known. The difference between FINRISK and Whitehall II cohorts was statistically significant for each baseline variable.

During follow-up, 194 liver-related outcomes were recorded (127 among men and 67 among women) in the FINRISK cohort, and 94 liver-related outcomes (66 among men and 28 among women) in Whitehall II.

3.1 | Diabetes increases the risk of liver-related outcomes

Subjects with diabetes had an approximately two-fold higher risk for liver-related outcomes compared with subjects without diabetes when adjusted for age and sex (HR, 1.92; 95% CI, 1.39–2.66; $p < .001$ in FINRISK and HR, 2.37; 95% CI, 1.52–3.71; $p < .001$ in Whitehall II) (Table 2). The association remained similar in both cohorts also after adjusting for age, sex, BMI, weekly alcohol use and smoking status (HR, 1.50; $p = .024$ and HR, 2.01; $p = .004$ respectively).

According to the PAF analyses, diabetes explained approximately 12%–14% of the risk for liver-related outcomes after 10 and 20 years of follow-up (Table 2). This finding was similar in the FINRISK and the Whitehall II cohorts (Figure 1). After adjusting for multiple confounders, the PAF estimate was 8% in FINRISK and 13% in Whitehall II (Table 2). As a comparison, the multivariate PAF analysis of baseline obesity for liver-related outcomes was 14% in the FINRISK and 16% in the Whitehall II (Table Table S2). As expected, the adjusted PAF of baseline alcohol risk use for liver-related outcomes was even higher: 30% in the FINRISK and 22% in the Whitehall II (Table Table S2).

In subgroup analysis (only in the FINRISK cohort), the risk for advanced non-alcoholic liver disease and HCC was increased in individuals with diabetes (HR, 2.42; $p < .001$ and HR, 3.03; $p = .001$ respectively) (Table 2). The association was only borderline significant after adjusting for multiple confounders (HR, 1.70; $p = .058$ for non-alcoholic liver disease and HR 1.99; $p = .058$ for HCC). The 10- and 20-year PAFs of diabetes for the non-alcoholic liver disease were approximately 18% and for HCC 26% after adjusting for age and sex (Table 2). After adjusting for multiple covariates, the 10- and 20-year PAF analyses were borderline significant for both non-alcoholic liver disease and HCC (PAF 12%; $p = .085$ and PAF 18%; $p = .078$–$.079$ respectively).

3.2 | Alcohol use and obesity modify the population attributable fraction of diabetes for liver outcomes

Next, we analysed PAF in different subgroups based on alcohol use and BMI in both cohorts. In the FINRISK, for individuals reporting

TABLE 2 The association of diabetes with all liver outcomes by Cox regression analysis and population attributable fraction analysis

	FINRISK			Whitehall II		
	n	Model 1	Model 2	n	Model 1	Model 2
All	28 787			7855		
Subjects with diabetes	2203			307		
Liver events	194			94		
HR (95% CI)		1.92 (1.39–2.66), $p < .001$	1.50 (1.05–2.12), $p = .024$		2.37 (1.52–3.71), $p < .001$	2.01 (1.26–3.24), $p = .004$
10-year PAF (95% CI)		12.27 (5.03–19.51), $p < .001$	8.15 (0.19–16.11), $p = .045$		14.81 (4.89–24.73), $p = .003$	13.26 (2.56–23.97), $p = .055$
20-year PAF (95% CI)		12.08 (4.98–19.19), $p < .001$	7.86 (.23–15.49), $p = .044$		14.70 (4.88–24.52), $p = .050$	12.85 (2.53–23.17), $p = .053$
Non-alcoholic	67					
HR (95% CI)		2.42 (1.46–4.02), $p < .001$	1.70 (0.98–2.96), $p = .058$		–	–
10-year PAF (95% CI)		18.31 (5.65–30.98), $p = .005$	12.27 (−1.71 to 26.26), $p = .085$		–	–
20-year PAF (95% CI)		18.18 (5.63–30.73), $p = .005$	12.14 (−1.67 to 25.95), $p = .085$		–	–
Liver cancer	32					
HR (95% CI)		3.03 (1.55–5.90), $p = .001$	1.99 (0.98–4.06), $p = .058$		–	–
10-year PAF (95% CI)		26.51 (7.26–45.76), $p = .007$	18.72 (−2.17 to 39.62), $p = .079$		–	–
20-year PAF (95% CI)		26.41 (7.24–45.58), $p = .007$	18.49 (−2.10 to 39.09), $p = .078$		–	–

Note: Model 1 adjusted for age and sex.Model 2 adjusted for age, sex, BMI, weekly alcohol use and smoking status.

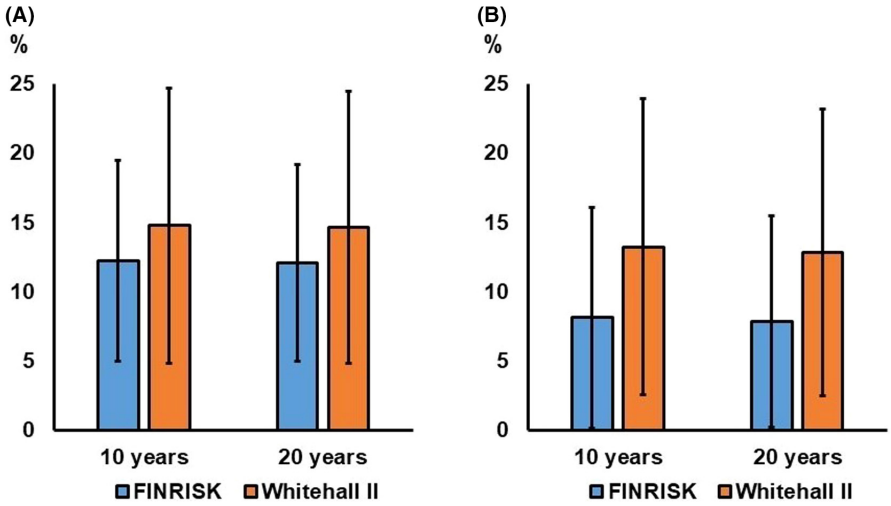

FIGURE 1 Population attributable fraction of diabetes for liver-related outcomes in the FINRISK and Whitehall II cohorts. The analysis is adjusted for age and sex in (A) and for age, sex, BMI, weekly alcohol use and smoking status in (B).

TABLE 3 The association of diabetes with all liver outcomes by Cox regression analysis and population attributable fraction analysis in the FINRISK and Whitehall II cohort subgroups

	FINRISK	Whitehall II
No alcohol risk drinking, n	23 562	7177
Subjects with diabetes, n	3170	1040
Liver events, n	110	69
HR (95% CI)	1.74 (1.12–2.72), $p = .014$	2.57 (1.53–4.32), $p < .001$
10-year PAF (95% CI)	10.25 (0.75–19.75), $p = .034$	17.10 (4.81–29.40), $p = .006$
20-year PAF (95% CI)	10.13 (0.77–19.49), $p = .034$	16.99 (4.80–29.18), $p = .006$
Alcohol risk drinking, n	2930	678
Subjects with diabetes, n	455	86
Liver events, n	69	25
HR (95% CI)	2.13 (1.25–3.62), $p = .005$	2.06 (0.84–5.03), $p = .114$
10-year PAF (95% CI)	15.12 (2.52–27.72), $p = .019$	10.39 (−6.17–26.95) $p = .219$
20-year PAF (95% CI)	14.45 (2.48–26.41), $p = .018$	10.11 (−5.88–26.10), $p = .215$
BMI <25 kg/m2, n	10 805	3336
Subjects with diabetes, n	519	306
Liver events, n	50	23
HR (95% CI)	2.45 (1.04–5.80), $p = .041$	1.53 (0.53–4.38), $p = .430$
10-year PAF (95% CI)	8.79 (−2.87 to 20.45), $p = .140$	4.20 (−7.95–16.35), $p = .498$
20-year PAF (95% CI)	8.66 (−2.76 to 20.08), $p = .137$	4.18 (−7.89–16.24), $p = .497$
BMI > 25 kg/m^2, n	17 694	4135
Subjects with diabetes, n	3377	777
Liver events, n	142	71
HR (95% CI)	1.83 (1.28–2.61), $p < .001$	2.71 (1.60–4.58), $p < .001$
10-year PAF (95% CI)	13.07 (4.25–21.89), $p = .004$	21.26 (6.88–35.64), $p = .004$
20-year PAF (95% CI)	12.87 (4.21–21.53), $p = .004$	21.10 (6.84–35.36), $p = .004$

Note: Adjusted for age and sex.Alochol risk drinking = baseline weekly alcohol > 210 g for men and >140 g for women.

alcohol risk drinking (≥140 g/week for women and ≥210 g/week for men), the 10-year PAF of diabetes for liver-related outcomes was 15% ($p = .019$) compared with 10% ($p = .034$) in individuals without alcohol risk drinking. In overweight/obese persons, the 10-year PAF was 13% ($p = .004$), whereas, in normal-weight persons, PAF was only 9% (non-significant) in the FINRISK (Table 3). A similar subgroup analysis was performed in the Whitehall II data, though the sample size was considerably smaller. In individuals reporting no alcohol risk drinking or were overweight, the 10-year PAF of diabetes for liver-related outcomes was 17% ($p < .001$) and 21% ($p = .004$) respectively

TABLE 4 Associations of family history of diabetes with all liver outcomes by Cox regression analysis

	FINRISK		Whitehall II	
	Model 1	Model 2	Model 1	Model 2
Mother with diabetes	1.43 (1.01–2.03), $p = .044$	1.52 (1.06–2.17), $p = .022$	2.04 (1.00–4.19), $p = .051$	2.06 (0.99–4.27), $p = .052$
Father with diabetes	0.84 (0.48–1.48), $p = .540$	0.81 (0.44–1.46), $p = .477$	0.48 (0.12–1.98), $p = .309$	0.47 (0.11–1.93), $p = .292$
Either mother or father or both parents with diabetes	1.23 (0.88–1.72), $p = .235$	1.25 (0.88–1.77), $p = .207$	1.26 (0.74–2.14), $p = .390$	1.23 (0.71–2.12), $p = .466$
Both mother and father with diabetes	1.10 (0.35–3.47), $p = .868$	1.12 (0.35–3.52), $p = .851$	NS	NS
Sibling with diabetes	0.98 (0.60–1.61), $p = .937$	0.88 (0.52–1.51), $p = .650$	1.34 (0.66–2.71), $p = .413$	1.52 (0.75–3.09), $p = .247$

Note: Numbers are HR (95% CI).Model 1 is adjusted for age and sex.Model 2 is adjusted for age, sex, BMI, weekly alcohol use and smoking status.
Abbreviation: NS, non-significant.

(Table 3). However, the analysis including alcohol risk drinkers and subjects with BMI under 25 kg/m^2 were statistically non-significant preventing direct comparison of outcomes between subgroups.

3.3 | Family history of diabetes associated with the risk of liver-related outcomes

In the analyses of the effect of family history of diabetes on the risk for liver-related outcomes in the FINRISK and the Whitehall II cohorts, we found that maternal history of diabetes increased the risk of liver outcomes (HR, 1.43; $p = .044$ and HR, 2.04; $p = .051$ respectively) (Table 4). Results were similar in the multivariate model in FINRISK (HR, 1.52; $p = .022$) and Whitehall II (HR, 2.06; $p = .052$). However, neither paternal diabetes nor sibling diabetes increased the risk for liver outcomes.

4 | DISCUSSION

Based on two large general population cohorts from Finland and UK, we estimate that approximately 12%–14% of severe liver-related outcomes are attributable to diabetes. Our PAF estimates ranged from 8% to 26% depending on the cohort, subgroup, and the level of covariate adjustment. Finally, we found that a maternal history of diabetes was associated with liver-related outcomes, whereas a paternal or sibling history of diabetes was not.

It is known that there is a strong association between diabetes and advanced liver diseases such as cirrhosis and HCC. This has been described both in clinical and population-based cohorts.[5,12,22,23] We confirmed this finding in two large differing population cohorts. Furthermore, PAF analyses brought additional information about the effect size of diabetes for liver-related outcomes at the population level. Recently, a PAF estimate of 5.6% for type 2 diabetes in predicting advanced NAFLD was reported from UK Biobank data, but this study focused only on NAFLD.[24]

The aetiology of chronic liver disease is often multifactorial. A PAF estimate of over 10% of a single factor, such as diabetes, is generally considered potentially interesting for future prevention strategies. On the other hand, although diabetes is an important risk factor for NAFLD,[25] if screening of individuals at risk were performed only in those with diabetes, the majority of individuals at risk would be missed. Our supplementary PAF analysis of obesity, alcohol risk use and advanced liver disease supports this conclusion. A holistic approach is needed when assessing an individual's risk for future severe liver disease.

Our analyses indicate that diabetes explains a notable portion of liver cancer risk in the general population (PAF 26%), in line with results from another cohort.[26] The PAF of diabetes was lower for advanced non-alcohol-related liver disease (PAF 18%), and this was also seen in a study by Jamialahmadi et al. In our analyses, PAF estimates of diabetes for advanced non-alcohol-related liver disease and liver cancer were lower after multiple adjustments (PAF 12% and 18% respectively) which indicates that some of the risk effect of diabetes for liver disease may be owing to confounding from alcohol use, smoking and/or BMI.

In the FINRISK cohort, the HR and PAF estimates of diabetes were particularly high among alcohol risk drinkers compared with non-risk drinkers (HR 2.13 vs. 1.74 and PAF 15% vs. 10% respectively). This is inline with the recent study of excessive alcohol use and the risk of severe liver disease in diabetics[27] and highlights the hazardous synergism between these two conditions for clinical liver disease.[11,12,28] Furthermore, we noticed that the PAF of diabetes was higher in subjects with BMI over 25 kg/m^2 compared with normal-weight subjects (PAF 13% vs. 9%). However, these observations could not be repeated in the Whitehall II data probably owing to the smaller sample size. In general, persons with alcohol risk drinking or overweight tend to have worse glycemic control compared with non-risk drinkers and normal-weight persons.[29,30] Furthermore, worse glycemic control has been associated with increased liver fibrosis,[31] which might explain the higher PAFs in the FINRISK cohort.

Interestingly, when analysing the association between family history of diabetes and liver-related outcomes, we found that only

maternal history of diabetes was associated with liver-related outcomes. In the Whitehall II cohort, the risk estimates (hazard ratios) were even higher but only borderline significant. This is most likely the issue of small sample size and underpowered data. Similar findings with a family history of diabetes and increased risk of NASH have been reported previously, but maternal/paternal inheritance was not specified in these studies.[8,32] Mitochondria are maternally inherited and mitochondrial function is important in the pathophysiology of chronic liver disease.[33,34] Thus, it is possible that mitochondrial genomics and unfavourable mitochondrial haplotypes may explain this link, but this needs further study. A potential confounder might be that diabetes is better diagnosed in women since women are tested during pregnancy and women tend to consult healthcare professionals more often than men do.[35]

Strengths of this study include the large cohorts of the Finnish and British general populations and the ability to capture not only baseline diabetes status but also incident diabetes cases from comprehensive nationwide registries (FINRISK) and follow-up clinical examinations (Whitehall II). Furthermore, the similarity of the results in two separate and demographically varying population-based cohorts strengthens our findings' validity.

Study limitations include the relatively low number of liver outcomes, especially in subgroup analyses, which may cause false-negative results (type II errors). Second, liver-related outcomes were based on records in national registries, omitting undiagnosed liver disease and less severe cases that may have been largely dealt with in primary care. However, this is probably not a major issue because we specifically wanted to examine complicated liver disease (liver disease requiring hospitalization, HCC and liver-related death). Third, unmeasured or incompletely measured confounding may exist despite multivariable adjustments and we were unable to adjust for time-dependent confounding. In this regard, the age- and sex-adjusted analyses may provide better estimates of the importance of diabetes for population liver disease. Nonetheless, direct conclusions on causality should be avoided, and we did not engage in mediation analyses.

We conclude that approximately 12%–14% of severe liver-related outcomes are attributable to diabetes at the population level. The association between maternal, but not paternal, diabetes history and liver-related outcomes might indicate a mitochondrial genetic mechanism, but this requires further study.

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CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

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ETHICS APPROVAL STATEMENT

The FINRISK studies were approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District and conducted according to the Declaration of Helsinki. Previously, the studies were approved by the institutional review board of the National Public Health Institute. The Whitehall II study was approved by the London-Harrow Research Ethics Committee and the Scotland Research Ethics Committee.

PATIENT CONSENT STATEMENT

All subjects provided informed consent for the study and for future registry linkage.

ORCID

Miika Vuorinen https://orcid.org/0000-0002-0399-4931
Ville T. Männistö https://orcid.org/0000-0002-0735-400X
Fredrik Åberg https://orcid.org/0000-0002-3833-0705

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SUPPORTING INFORMATION

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