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ORIGINAL ARTICLE

Retrospective Study

Risk factors for major gastrointestinal bleeding in the general population in Finland

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Abstract

BACKGROUND

Data on non-drug related risk-factors for gastrointestinal bleeding (GIB) in the general population are limited, especially for life-style factors, clinical measurements and laboratory parameters.

AIM

To identify and investigate non-drug risk factors for major GIB in the general population of Finland.

METHODS

We performed a retrospective cohort study using data from the FINRISK health examination surveys, which have been conducted every 5 years across Finland from 1987 to 2007. Participants were adults aged 25 years to 74 years, excluding those with a previous hospitalization for GIB. Follow-up from enrollment was performed through linkage to national electronic health registers and ended at an event of GIB that led to hospitalization/death, death due to any other cause, or after 10 years. Covariates included demographics, socioeconomic and lifestyle factors, clinical measurements, laboratory parameters and comorbidities. Variable selection was undertaken using Least Absolute Shrinkage and Selection Operator

(LASSO) and factors associated with GIB were identified using Cox regression.

RESULTS

Among 33,508 participants, 403 (1.2%) experienced GIB [256 men (63.5%); mean age, 56.0 years (standard deviation (SD) ± 12.1)] and 33105 who did not experience GIB [15768 men (47.6%); mean age, 46.8 (SD ± 13) years], within 10 years of follow-up. Factors associated with a significantly increased risk of GIB were baseline age [per 10-year increase; hazard ratio (HR) 1.62, 95% confidence interval (CI): 1.42-1.86], unemployment (HR: 1.70, 95%CI: 1.11-2.59), body mass index (BMI) (HR: 1.15, 95%CI: 1.01-1.32), gamma-glutamyl transferase (GGT) (HR: 1.05, 95%CI: 1.02-1.09), precursors of GIB (HR: 1.90, 95%CI: 1.37-2.63), cancer (HR: 1.47, 95%CI: 1.10-1.97), psychiatric disorders (HR: 1.32, 95%CI: 1.01-1.71), heart failure (HR: 1.46, 95%CI: 1.04-2.05), and liver disorders (HR: 3.20, 95%CI: 2.06-4.97). Factors associated with a significantly decreased risk of GIB were systolic blood pressure (SBP) (HR: 0.78, 95%CI: 0.64-0.96), 6-10 cups of coffee a day (HR: 0.67, 95%CI: 0.46-0.99), or > 10 cups (HR: 0.43, 95%CI: 0.23-0.81).

CONCLUSION

Our study confirms established risk-factors for GIB and identifies potential risk-factors not previously reported such as unemployment, BMI, GGT, SBP and coffee consumption.

Key Words: Risk factors; Gastrointestinal hemorrhage; General population; Finland; Life style; Population health

Core Tip: This retrospective study of 33508 Finnish survey participants aimed to identify and investigate non-drug factors associated with the risk of major gastrointestinal bleeding (GIB) in the general population in Finland. Aside from established risk factors, our study identified unemployment, body mass index and gamma-glutamyl transferase enzyme were all associated with increased risk of major GIB. Systolic blood pressure and coffee consumption were associated with a decreased risk of major GIB.

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INTRODUCTION

Gastrointestinal bleeding (GIB) is one of the most frequent types of major bleeding events seen in clinical practice and it can be potentially life-threatening if not managed appropriately[1]. Although several studies have investigated risk factors of GIB, these have largely evaluated associations with medications[2-5] or have been conducted in specific population groups, such as those who were critically ill[6-8]. Only a few have investigated potential associations with lifestyle factors such as smoking, alcohol consumption, and physical activity or laboratory parameters[9-11]. Furthermore, several studies on this topic have lacked information on lifestyle factors, clinical measurements, and laboratory parameters as well as long longitudinal follow-up. To identify independent risk factors for GIB, it is important to understand the association of these additional parameters on the risk of GIB when taken in account together with demographic data and comorbidities in the general population. Establishing independent risk factors for GIB is important because it will help to identify patients at high risk of GIB and to better target preventative interventions. In addition, it would be particularly relevant for designing future studies on GIB. Using data from FINRISK surveys and national health registers, we aimed to identify and investigate risk factors for major GIB in the general population of Finland.

MATERIALS AND METHODS

Ethics statement

The National FINRISK Study surveys (started in 1972) followed the EHES (European Health Examination Survey)[12] and the MONICA (Monitoring of Trends and Determinants in Cardiovascular

Disease)[13] project protocols and were approved by the ethics committee of the Finnish Institute of Health and Welfare and the Coordinating Ethical Committee of Helsinki and Uusimaa Hospital District in Finland (THL/66/0.05.00/2015). All participants in the FINRISK surveys provided their informed consent at the time of enrollment and the study was conducted following the principles of the Declaration of Helsinki. Data from the participants was pseudonymized for this study and the secondary use of the survey data was approved by the Finnish Institute of Health and Welfare in 2017.

Study design, data source, and study population

This retrospective cohort study used data from the FINRISK health examination surveys - a series of large population-based, cross-sectional surveys (with 6000 to 8800 participants per survey) carried out every 5 years to determine the risk factors for chronic, noncommunicable diseases. Survey participants were randomly chosen using the population register of Finland to obtain a representative sample of individuals across several geographic regions of Finland; those who responded to the invitation were subsequently enrolled in the study as participants in the first quarter of each survey year. From each geographical area, the surveys enrolled at least 250 subjects of each sex and 10-year age group. From the 1972 survey to the 2007 survey, the participation rate gradually decreased from approximately 80% to 65%[14].

Using data from the 1987, 1992, 1997, 2002, 2007 FINRISK survey cohorts, we identified 33796 unique participants aged 25 years to 74 years. Of these, 288 were excluded due to having hospitalization for GIB before baseline, resulting in a final cohort of 33508 individuals. Using record linkage of FINRISK participants to nationwide electronic health care registers, including the hospital discharge register and causes of death register, we identified incident cases of major GIB. These national registers cover virtually all persons living in Finland. The possibility of linking demographics, lifestyle factors, clinical measurements and laboratory parameters collected in the FINRISK surveys with national health registers increased the granularity of the dataset. The follow-up period was from the date of enrollment in the FINRISK survey to the incidence of GIB that led to hospitalization/death, death from any cause, or a maximum of 10 years, whichever occurred first. The overall design of the study is presented in Supplementary Figure 1.

Study outcome

Major GIB was defined as GIB that led to hospitalization or GIB-specific death (see Supplementary Table 1 for codes), recorded as either the main or the top three contributing factors for the hospitalization, or the underlying, direct, or contributing cause of death. We followed participants from survey enrollment for a maximum of 10 years to allow equal follow-up time for all survey cohorts to observe GIB. In the previous analyses, we have shown that the overall age standardized incidence rate of GIB in the FINRISK cohorts to be 2.10 per 1000 person-years [men: 2.62 per 1000 person-years (95%CI: 2.40-2.86) and women: 1.62 per 1000 person-years (95%CI: 1.45-1.81)][15].

Covariates

Baseline data collected at enrollment into FINRISK surveys included demographic data (age, sex, year of enrollment and region); socioeconomic factors (marital status, occupation, education); lifestyle factors (smoking status, alcohol consumption, coffee consumption, body mass index [BMI], waist hip ratio [WHR], physical activity); blood pressure measurements (systolic [SBP] and diastolic blood pressure [DBP]); and laboratory parameters (total cholesterol, high density lipoprotein cholesterol [HDL], gamma-glutamyl transferase enzyme [GGT]).

Morbidities were identified in the participant's history any time before the GIB or any time before the end of follow-up for participants without GIB. These were obtained from the hospital discharge register, causes of death register, as well as from drug reimbursement register, and prescription register using drugs as proxies for chronic conditions. Conditions were identified using the International Classification of Diseases, Ninth Revision (ICD-9) or the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes as well as prescription codes identified using Anatomical Therapeutic Chemical (ATC) codes and database specific codes of the Finnish Social Insurance. Morbidities included any cancer diagnosis, any psychiatric illness, cardiovascular diseases (stroke, venous thromboembolism, ischemic heart disease, valvular heart disease, atrial fibrillation, peripheral artery disease, heart failure, high blood pressure), a composite of precursors of GIB without bleeding (including gastritis, intestinal diseases, esophageal varices, esophagitis, hemorrhoids, colitis and Crohn's disease), osteoarthritis, connective tissue disorders, diabetes, chronic obstructive pulmonary disease, asthma, liver disorders and anemia (see Supplementary Table 2 for codes).

Statistical analyses

Participants' characteristics were summarized using counts and percentages for categorical variables and means with standard deviation (SD) for continuous variables. We conducted univariate Cox regression using all covariates. We used the Least Absolute Shrinkage and Selection Operator (LASSO) method for variable selection, which provides a relevant and interpretable group of variables from a larger set of covariates including potentially multicollinear variables[16]. LASSO regression maximizes

the partial likelihood of the regression coefficients by imposing a constraint on the sum of the absolute value of all regression coefficients in the model producing coefficients that are exactly zero, thereby regulating the impact of a coefficient in the regression[16]. This effectively excludes some variables which are unnecessary/uninfluential without the need for formal statistical testing thereby reducing the likelihood of overfitting using cross validation. Moreover, the LASSO method is less variable than the stepwise approach and yields interpretable models. The Cox LASSO regression including all the available variables showed the best model could be fitted between 12 to 39 variables (see Supplementary Figure 2). Further, we fitted a Cox proportional hazards model using variables selected by LASSO, *i.e.*, we did not include variables whose coefficients shrank towards zero. Using this approach, we obtained hazard ratios (HRs) with 95% confidence intervals (CI) for the variables in the final model[17]. Using statistical tests and graphical diagnostics, we checked the proportional hazards assumption on the *scaled Schoenfeld residuals*. Continuous variables in the Cox model were standardized by subtracting the value of the variable from its mean and dividing by its SD. For interpretation, it provides a change in risk when the value of the variable changes by one SD. There were few participants with missing baseline data (< 3%); they were excluded from the analysis and no imputations were performed. All statistical analyses were done with R, version 3.6.1 using 'glmnet' package (R Foundation for Statistical Computing).

RESULTS

Characteristics

Of the total 33508 participants, 403 (1.2%) experienced at least one GIB within the maximum 10 years of follow-up. Baseline characteristics of the study cohort are summarized in Table 1. The mean age at enrollment was 56 years (SD ± 12.1) for participants with an incident of GIB and 46.8 years (SD ± 13.0) for those who did not experience GIB. Of the participants experiencing GIB compared to those who did not have GIB, the majority were male (63.5% *vs* 47.6%), from the western region (40.4% *vs* 38.0%), single (31.0% *vs* 26.0%), a current/ex-smoker (56.1% *vs* 46.2%), a heavy alcohol drinker (25.1% *vs* 20.8%), consumed 6-10 cups of coffee per day (21.3% *vs* 27.2%) and undertook moderate-to-heavy physical activity (12.9% *vs* 21.4%). Overall, participants with GIB had a higher prevalence of comorbidities than participants without GIB as seen in Table 2, except osteoarthritis (5.0% *vs* 6.2%) which was lower. Participants developing a GIB also had a higher mean BMI (28.3 kg/m^2, SD ± 5.19 *vs* 26.6 kg/m^2, SD ± 4.61), mean WHR (0.93, SD ± 0.1 *vs* 0.88, SD ± 0.1), and mean SBP (141 mmHg, SD ± 21.7 *vs* 136 mmHg, SD ± 19.8) than those who did not experience a GIB. Of the laboratory parameters, GGT appeared to be higher in participants with GIB (59.5 U/L, SD ± 141 *vs* 31.2 U/L SD ± 45). Participants with GIB had more precursors of GIB (11.9% *vs* 4.5%) compared to participants without GIB. The results of univariate analyses showing each variable's association with the risk of major GIB are presented in Table 3.

Risk factors for major GIB

The LASSO method identified the most important predictors from larger set of variables. Variables with negative coefficients exhibit decreased risk, positive coefficients exhibit increased risk, and coefficient with value zero are the least important predictor variables in the model to predict gastrointestinal bleeding and can be removed from the final model. The aim of LASSO method is model prediction by selecting the most important predictor variables and therefore statistical significance of regression coefficients is not computed here (see Supplementary Table 3). Using these results from LASSO, we excluded variables such as DBP, HDL, VTE and Inflammatory connective tissue diseases from the final Cox model. Categorical variables for which one of the strata had a zero coefficient were kept in the final model.

Increased risk of major GIB

In terms of socio-demographics and lifestyle factors, the Cox regression showed that baseline age (HR: 1.62, 95%CI: 1.42-1.86, per 10-year increase), unemployment (HR: 1.70, 95%CI: 1.11-2.59), and higher BMI (HR: 1.15, 95%CI: 1.01-1.32) were all associated with an increased risk of GIB (Table 3). Among clinical variables, higher GGT levels (HR: 1.05, 95%CI: 1.02-1.09), having ≥ 1 precursor of GIB (HR: 1.90, 95%CI: 1.37-2.63), previous cancer (HR: 1.47, 95%CI: 1.10-1.97), psychiatric disorders (HR: 1.32, 95%CI: 1.01-1.71), heart failure (HR: 1.46, 95%CI: 1.04-2.05), and liver disorders (HR: 3.20, 95%CI: 2.06-4.97) were all associated with an increased risk of GIB. There was no clear evidence that history of cardiovascular disease was associated with the risk of major GIB.

Decreased risk of major GIB

SBP (HR: 0.78, 95%CI: 0.64-0.96) as well as drinking 6-10 cups of coffee a day (HR: 0.67, 95%CI: 0.46-0.99) or more than 10 cups of coffee a day (HR: 0.43, 95%CI: 0.23-0.81), and history of osteoarthritis (HR: 0.39, 95%CI: 0.24-0.65) were all associated with a decreased risk of GIB.

Table 1 Baseline characteristics for participants with and without major gastrointestinal bleedings during follow-up

Baseline characteristics	GIB, *n* = 403	No GIB, *n* = 33105	Overall, *n* = 33508
Age at baseline, mean (SD)	56.0 (12.1)	46.8 (13.0)	46.9 (13.0)
Sex			
Male	256 (63.5)	15768 (47.6)	16024 (47.8)
Female	147 (36.5)	17337 (52.4)	17484 (52.2)
Yr of enrollment, Q1			
1987	45 (11.2)	5872 (17.7)	5917 (17.7)
1992	51 (12.7)	5371 (16.2)	5422 (16.2)
1997	126 (31.3)	7857 (23.7)	7983 (23.8)
2002	108 (26.8)	8155 (24.6)	8263 (24.7)
2007	73 (18.1)	5850 (17.7)	5923 (17.7)
Region[1]			
West	163 (40.4)	12570 (38.0)	12733 (38.0)
East	240 (59.6)	20535 (62.0)	20775 (62.0)
Marital status			
Married, cohabiting, or registered partnership	278 (69.0)	24391 (73.7)	24669 (73.6)
Single, separated, divorced, or widow	125 (31.0)	8623 (26.0)	8748 (26.1)
Missing	0 (0.0)	91 (0.3)	91 (0.3)
Occupation			
Non-manual (office/studying)	102 (25.3)	15889 (48.0)	15991 (47.7)
Manual (factory/construction/farming/forestry)	62 (15.4)	6692 (20.2)	6754 (20.2)
Family/housewife/pensioner	191 (47.4)	8033 (24.3)	8224 (24.5)
Unemployed	37 (9.2)	2006 (6.1)	2043 (6.1)
Missing	11 (2.7)	485 (1.5)	496 (1.5)
Education in tertiles[2]			
Low	128 (31.8)	10029 (30.3)	10157 (30.3)
Moderate	113 (28.0)	10735 (32.4)	10848 (32.4)
High	144 (35.7)	11619 (35.1)	11763 (35.1)
Missing	18 (4.5)	722 (2.2)	740 (2.2)
Smoking			
Never	168 (41.7)	17381 (52.5)	17549 (52.4)
Ex-smoker	121 (30.0)	7028 (21.2)	7149 (21.3)
Smoker	105 (26.1)	8273 (25.0)	8378 (25.0)
Missing	9 (2.2)	423 (1.3)	432 (1.3)
Alcohol consumption in grams per week			
Non-drinker	164 (40.7)	12548 (37.9)	12712 (37.9)
Mild (0.1 g to 36.9 g)	65 (16.1)	6835 (20.6)	6900 (20.6)
Moderate (37 g to 86.9 g)	54 (13.4)	5914 (17.9)	5968 (17.8)
Heavy (≥ 87g)	101 (25.1)	6879 (20.8)	6980 (20.8)
Missing	19 (4.7)	929 (2.8)	948 (2.8)
Coffee consumption per day, cups			
0	38 (9.4)	2858 (8.6)	2896 (8.6)

1–5	267 (66.3)	20294 (61.3)	20561 (61.4)
6–10	86 (21.3)	9008 (27.2)	9094 (27.1)
> 10	4 (1.0)	637 (1.9)	641 (1.9)
Missing	8 (2.0)	308 (0.9)	316 (0.9)
Physical activity			
Minimal to mild	335 (83.1)	25306 (76.4)	25641 (76.5)
Moderate to heavy	52 (12.9)	7095 (21.4)	7147 (21.3)
Missing	16 (4.0)	704 (2.1)	720 (2.1)
Body mass index in kg/m^2, mean (SD)	28.3 (5.2)	26.6 (4.6)	26.6 (4.6)
Missing	10 (2.5)	389 (1.2)	399 (1.2)
Waist-hip ratio, mean (SD)	0.93 (0.1)	0.88 (0.1)	0.88 (0.1)
Missing	5 (1.2)	404 (1.2)	409 (1.2)
Systolic blood pressure in mm Hg, mean (SD)	141.0 (22)	136.0 (20)	136.0 (20)
Missing	2 (0.5)	268 (0.8)	270 (0.8)
Diastolic blood pressure in mm Hg, mean (SD)	83.5 (12.7)	81.0 (11.7)	81.0 (11.7)
Missing	2 (0.5)	271 (0.8)	273 (0.8)
Total cholesterol in mmol/L, mean (SD)	5.69 (1.09)	5.58 (1.12)	5.58 (1.12)
Missing	5 (1.2)	347 (1.0)	352 (1.1)
High density lipoprotein in mmol/L, mean (SD)	1.39 (0.44)	1.44 (0.38)	1.44 (0.38)
Missing	5 (1.2)	347 (1.0)	352 (1.1)
Gamma-glutamyl transferase in U/L, mean (SD)	59.5 (141)	31.2 (45.0)	31.5 (47.4)
Missing	5 (1.2)	356 (1.1)	361 (1.1)

[1]West Finland includes Turku and Loimaa as well as Helsinki and Vantaa. East Finland includes North Karelia, North Savo, Oulu, and Lapland.
[2]Educational tertiles were calculated according to years of education and were specific to the birth cohorts.
Data are *n* (%), unless otherwise indicated. GIB: Gastrointestinal bleeding; SD: Standard deviation; IQR: Interquartile range.

DISCUSSION

Our large population-based study enabled the evaluation of a wide range of potential risk factors for GIB in the general population, including demographics, socioeconomic and lifestyle factors, comorbidities, clinical measurements and laboratory parameters. Aside from confirming previously known risk factors for major GIB, we also identified unemployment, higher BMI, and higher levels of GGT as associated with a significantly increased risk of GIB, whereas increased daily coffee consumption (> 5 cups) as well as higher SBP were associated with a significantly decreased risk of GIB.

While many studies have investigated the effect of coffee on GI tract including GI cancer prevention, we believe ours is the first to investigate its association with GIB, with 29% of our study population with daily coffee consumption of > 5 cups[18]. A recent review by Iriondo-DeHond *et al*[18], outlined potential mechanisms and summarized the current evidence on the effects of individual coffee components on GI tract concluding that support for a possible causal association is insufficient. Nonetheless, several meta-analyses have reported a protective effect of coffee consumption on colon cancer[19-24] which is a major cause of GIB. A few studies[25-28] have shown that low SBP is associated with an increased risk of GIB, which supports the protective effect of high SBP seen in our study. Our results indicated that approximately 22 units decrease in SBP would increase the risk of GIB by 15%. Therefore, apart from diagnosis of hypertension, SBP values should be considered and included in the analyses of GIBs whenever available. Level of education was not associated with an increased risk for major GIBs, in contrast to being unemployed which is in line with previous research consistently showing that unemployment is associated with poor health[29,30]. Increase in age has been consistently associated with increased risk of major GIBs in the literature as in our study[28,31]. In relation to anthropometric measures, higher BMI was associated with an increased risk of GIB but not WHR or low physical activity and we are unaware of any other studies that have evaluated these variables in this context. We found no association between alcohol consumption and the risk of major GIB, in contrast to previous studies on upper GIBs[32,33]. However, association with an increased risk of major GIB were seen with a history of liver disorders as well as high levels of GGT which can be caused by chronic

Table 2 Medical history in participants with and without gastrointestinal bleeding

Comorbidities	GIB, *n* = 403	No GIB, *n* = 33105	Overall, *n* = 33508
Precursors of GIBs[1]			
0	355 (88.1)	31621 (95.5)	31976 (95.4)
1	45 (11.2)	1399 (4.2)	1444 (4.3)
2	3 (0.7)	78.0 (0.2)	81.0 (0.2)
3	0 (0)	7.00 (0.0)	7.00 (0.0)
Any cancer	63 (15.6)	2421 (7.3)	2484 (7.4)
Any psychiatric disorders	104 (25.8)	4653 (14.1)	4757 (14.2)
Stroke including SAH	39 (9.7)	1239 (3.7)	1278 (3.8)
Venous thromboembolism	17 (4.2)	728 (2.2)	745 (2.2)
Ischemic heart disease	101 (25.1)	3433 (10.4)	3534 (10.5)
Valvular heart disease	23 (5.7)	689 (2.1)	712 (2.1)
Atrial fibrillation	55 (13.6)	1512 (4.6)	1567 (4.7)
Peripheral artery disease	23 (5.7)	553 (1.7)	576 (1.7)
Heart failure	76 (18.9)	1810 (5.5)	1886 (5.6)
High blood pressure	128 (31.8)	6572 (19.9)	6700 (20.0)
Osteoarthritis	20 (5.0)	2062 (6.2)	2082 (6.2)
Inflammatory connective tissue diseases	29 (7.2)	1458 (4.4)	1487 (4.4)
Diabetes[2]	52 (12.9)	2390 (7.2)	2442 (7.3)
COPD	24 (6.0)	638 (1.9)	662 (2.0)
Asthma	54 (13.4)	3828 (11.6)	3882 (11.6)
Liver disorder	29 (7.2)	389 (1.2)	418 (1.2)
Anemia	6 (1.5)	70 (0.2)	76 (0.2)

[1]Includes conditions without gastrointestinal bleeding such as gastritis, intestinal diseases, esophageal varices, esophagitis, hemorrhoids, colitis, Crohn's disease.
[2]Excluding gestational diabetes.
Data are *n* (%). GIB: Gastrointestinal bleeding; COPD: Chronic obstructive pulmonary disease; SAH: Sub-arachnoid hemorrhage.

heavy alcohol consumption and is in line with the components of some GIB-risk scores[28].

Very few studies mostly focusing on upper GIBs have shown increased risk associated with smoking [32,34], however our multivariate analyses showed no association between self-reported smoking (ex- or current) and major GIB. In terms of morbidities, consistent with previous studies[28,35], a history of heart failure was associated with an increased risk of GIB. This could be related to the treatments and to the fact that heart failure often coexists with atrial fibrillation which is treated with anticoagulants. As medications commonly used to treat osteoarthritis - non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids - are thought to increase the risk of GIB[36,37], a number of possible explanations could account for our finding that osteoarthritis was associated with a decreased risk for GIB including that the patients with osteoarthritis were actively monitored, received better care and management of the disease, were prescribed PPI to prevent GIBs, or used other available treatments[38]. Although medications such as antiplatelet agents and anticoagulants, which are associated with an increased risk of GIBs[9] are often used to treat cardiovascular diseases, our study did not find an association between history of cardiovascular diseases and GIB. Our study suggests that the predictors of major GIBs in the general population might be slightly different than in critically ill populations or comorbid patients using multiple medications[3,4,6-8,11].

Strengths and limitations

Our study has several strengths. A key strength was the long follow-up (up to 10 years) of individuals from a large representative sample of the general population of Finland enabling identification of more than 400 incident cases of GIB. The loss to follow-up was minimal, and the data sources enabled us to incorporate a wide range of potential risk factors in our analyses. Missing data amongst the participants

Table 3 Multivariate analysis for the risk factors for major gastrointestinal bleeding

Variables	Univariate model, HR (95%CI)	Multivariate model, HR (95%CI)
Baseline age (10-yr increase)	1.83 (1.69–1.99)	1.62 (1.42–1.86)
Sex		
Male	1	1
Female	0.51 (0.42–0.63)	0.83 (0.59–1.17)
Yr of enrollment		
1987	1	1
1992	1.23 (0.83-1.84)	1.15 (0.74–1.79)
1997	2.10 (1.50–2.96)	1.36 (0.91–2.04)
2002	1.72 (1.21–2.43)	1.10 (0.72–1.68)
2007	1.66 (1.15–2.41)	0.90 (0.57–1.43)
Region[1]		
West Finland	1	1
East Finland	0.90 (0.74–1.10)	0.96 (0.77–1.20)
Marital status		
Married, cohabiting, or registered partnership	1	1
Single, separated, divorced, or widow	1.29 (1.04–1.59)	1.09 (0.86–1.38)
Occupation		
Non-manual (office/studying)	1	1
Manual (factory/ construction/ farming/ forestry)	1.45 (1.06–1.98)	1.25 (0.88–1.78)
Family/ housewife/ pensioner	3.90 (3.06–4.95)	1.26 (0.90–1.75)
Unemployed	2.92 (2.00–4.25)	1.70 (1.11–2.59)
Education[2]		
Low	1	1
Moderate	0.82 (0.64–1.06)	0.81 (0.62–1.06)
High	0.96 (0.76–1.22)	1.05 (0.80–1.38)
Smoking		
Never	1	1
Ex-smoker	1.80 (1.43–2.28)	1.18 (0.90–1.53)
Smoker	1.34 (1.05–1.71)	1.30 (0.97–1.74)
Alcohol consumption in grams per week		
Non-User	1	1
Mild (0.1 g to 36.9 g)	0.72 (0.54–0.96)	0.88 (0.66–1.19)
Moderate (37 g to 86.9 g)	0.69 (0.51–0.94)	0.76 (0.54–1.06)
Heavy (≥ 87 g)	1.13 (0.88–1.44)	1.02 (0.76–1.37)
Coffee consumption per day, cups		
0	1	1
1–5	1.00 (0.71–1.40)	0.72 (0.50–1.02)
6–10	0.72 (0.49–1.06)	0.67 (0.46–0.99)
> 10	0.48 (0.17–1.33)	0.43 (0.23–0.81)
Physical activity		
None to Mild	1	1

Moderate to Heavy	0.55 (0.41–0.73)	0.85 (0.62–1.16)
Body mass index standardized	1.38 (1.27–1.50)	1.15 (1.01–1.32)
Waist hip ratio standardized	1.70 (1.55–1.86)	1.18 (0.98–1.43)
Systolic blood pressure standardized	1.30 (1.19–1.42)	0.85 (0.76-0.96)
Diastolic blood pressure standardized	1.24 (1.13–1.37)	-
Total cholesterol standardized	1.10 (1.00–1.21)	0.94 (0.84–1.05)
High density lipoprotein standardized	0.86 (0.77–0.95)	-
Gamma-glutamyl transferase standardized	1.10 (1.08–1.12)	1.05 (1.02-1.09)
Precursors of GIB[3]		
0	1	1
≥ 1	9.44 (7.65–11.65)	1.90 (1.37–2.63)
Any cancer	2.66 (2.03–3.48)	1.47 (1.10–1.97)
Any psychiatric disorders	2.21 (1.77–2.77)	1.32 (1.01–1.71)
Stroke including SAH	2.98 (2.14–4.15)	1.31 (0.90–1.90)
Venous thromboembolism	2.04 (1.26–3.32)	-
Ischemic heart disease	3.14 (2.51–3.94)	1.16 (0.87-1.55)
Valvular heart disease	2.91 (1.91–4.44)	1.40 (0.88-2.25)
Atrial fibrillation	3.46 (2.60–4.60)	1.05 (0.73–1.51)
Peripheral artery disease	3.94 (2.59–6.00)	1.39 (0.87–2.23)
Heart failure	4.35 (3.39–5.58)	1.46 (1.04–2.05)
High blood pressure	1.92 (1.55–2.36)	0.90 (0.69–1.17)
Osteoarthritis	0.78 (0.50–1.23)	0.39 (0.24–0.65)
Connective tissue diseases	1.72 (1.18–2.51)	-
Diabetes[4]	1.97 (1.47–2.64)	0.76 (0.54–1.08)
Chronic obstructive pulmonary disease	3.57 (2.36–5.39)	1.26 (0.77–2.06)
Asthma	1.19 (0.89–1.58)	0.80 (0.58–1.11)
Liver disorder	6.95 (4.76–10.15)	3.20 (2.06–4.97)
Anemia	7.16 (3.20–16.04)	1.52 (0.48–4.83)

[1]West Finland includes Turku and Loimaa as well as Helsinki and Vantaa. East Finland includes North Karelia, North Savo, Oulu, and Lapland.
[2]Educational tertiles were calculated according to years of education and were specific to the birth cohorts.
[3]Includes conditions without gastrointestinal bleeding such as gastritis, intestinal diseases, esophageal varices, esophagitis, hemorrhoids, colitis, or Crohn's disease.
[4]Excluding gestational diabetes.
'-' indicates that the variable was not included in the final multivariate Cox model based on the results from LASSO.
CI: Confidence Interval; GIB: Gastrointestinal bleeding; HR: Hazard ratio; SAH: Subarachnoid hemorrhage.

was also minimal. Compared to stepwise selection of variables into the regression model, the LASSO method helped to address multicollinearity and to avoid overfitting. The LASSO approach also performed an internal validation by inbuilt cross-validation techniques, although an external validation of the newly proposed risk factors is still warranted. A small degree of misclassification of GIB is possible because the electronic health register data was collected for administrative purposes, however the magnitude is likely to be very small. We used hospital diagnoses as well as drug prescriptions to identify chronic conditions. Further, NSAIDs can be obtained over the counter and not recorded in the data sources, hence could not be included in our analyses. Also, due to the insufficient numbers of cases, factors such as hemophilia, thyroid disorders, pancreatitis and chronic kidney failure could not be investigated. Information on lifestyle factors such as smoking, and alcohol consumption are self-reported and might be under-reported. Lastly, the data on demographic, lifestyle, and laboratory parameters were only collected at baseline and no repeated measurements were conducted during the study period. Therefore, we could not account for lifestyle modifications on the risk of GI bleeding in our analyses.

Clinical implications and future research

In addition to previously established risk factors for GIB, we have identified additional potential independent risk factors for major GIB, further helping build the knowledge base on this topic. This will support in identifying patients at high risk of GIB. Further, this will support early interventions or counseling to prevent incident or recurrent GIBs as well as help in monitoring the prevalence of these risk factors. The results from our study are exploratory and future studies are required to establish causal associations and hopefully stimulate research of these factors in the general population which currently is scarce.

CONCLUSION

Our study showed that older age, unemployment, higher BMI, higher GGT levels, history of precursors of GIBs, cancer, psychiatric illness, heart failure and liver disorders were associated with an increased risk of major GIBs. Moreover, higher coffee consumption (> 5 cups per day) and higher SBP showed an inverse association with major GIB. These associations in the general population need to be confirmed by future research and other epidemiological studies.

ARTICLE HIGHLIGHTS

Research background

Limited information is available on the risk factors of gastrointestinal bleedings (GIB) in the general population. Previous research mainly focused on the population using specific medications such as antiplatelets, anticoagulants *etc.* or the critically ill population such as hospitalized patients or elderly. Therefore, we investigated the risk factors for major GIB using data representative of the general population having a high granularity of the data source and long-term follow-up of participants.

Research motivation

Many studies investigating risk factors of GIB lacked information on lifestyle factors, clinical measurements and laboratory parameters. We wanted to better understand the effect of these additional variables on GIB as well as how this affects established risk factors. Additionally, to better understand the factors that predict the risk of GIB in the presence of a multicollinear set of variables [*e.g.*, Body mass index (BMI), Waist-hip ratio (WHR) or physical activity].

Research objectives

The overall objective of the study was to identify and investigate new risk factors of major GIB in the general population of Finland considering established risk factors as well as demographics and morbidities. We were able to identify new risk factors of major GIB together with established risk factors which needs to be evaluated and confirmed by further research.

Research methods

We conducted a retrospective cohort study using record linkage of data from the FINRISK health examination surveys which are representative of the general population of Finland to the national electronic health registers with 10 years of follow-up. This linkage enabled us to include and investigate demographics, socioeconomic and lifestyle factors, clinical measurements, laboratory parameters, and comorbidities on the risk of major GIB. We further implemented Least Absolute Shrinkage and Selection Operator (LASSO) to select the most important predictor variables for model prediction and association of these predictor variables were evaluated using Cox regression. The novelty of using LASSO is that it helps in the variable selection and in excluding unnecessary/uninfluential variables from the model thus reducing the likelihood of overfitting a model. It also helps to address multicollinearity that can be problematic in the traditional forms of regression.

Research results

The main results of the study showed that baseline age, unemployment, and higher BMI, higher gamma-glutamyl transferase (GGT) levels, having ≥1 precursor of GIB, previous cancer, psychiatric disorders, heart failure and liver disorders were all associated with an increased risk of GIB. Systolic blood pressure, above average coffee consumption per day, and history of osteoarthritis were all associated with a decreased risk of GIB. This study adds to the scarce literature on risk factors on gastrointestinal bleeding in the general population. Additionally, results are hypothesis generating for the new risk factors identified in this study which must be confirmed by future mechanistic and epidemiological studies.

Research conclusions

This study identified new risk factors associated with major GIB which are unemployment, BMI, GGT, SBP and coffee consumption. Accounting for physical activity and waist-hip ratio, our study suggests that BMI is a better predictor of major GIB. Above average coffee consumption per day, which seems to be more common in Finland with the highest per capita coffee consumption in the world, was associated with a decreased risk of major GIB. Our study suggests that the risk factors of major GIBs might be slightly different in the general population than the at-risk population.

Research perspectives

Future mechanistic and epidemiological studies should evaluate these risk factors in different study populations or countries across the world to establish causal associations. This will further support in complementing and refining existing risk scores for major GIBs.

FOOTNOTES

Author contributions: Vora P, Brobert G and Salomaa V proposed the concept and design; Salomaa V and Pietila A supported in acquisition of the collected data; Vora P, Herrera R, Pietila A and Mansmann U performed the statistical analysis; Vora P drafted the manuscript; Vora P, Brobert G and Salomaa V obtained funding; Pietila A and Salomaa V provided the administrative, technical, and material support; Salomaa V, Mansmann U and Brobert G were responsible for supervision; All authors were involved in the interpretation of the results, critical revision of the manuscript and approved the final version of the article for publication.

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Institutional review board statement: The National FINRISK Study surveys started in 1972 were approved by the ethics committee of the Finnish Institute of Health and Welfare and the Coordinating Ethical Committee of Helsinki and Uusimaa Hospital District in Finland (THL/66/0.05.00/2015). Data from the participants were pseudonymized for this study, and the secondary use of the survey data was approved by the Finnish Institute of Health and Welfare in 2017.

Informed consent statement: All participants provided their informed consents at enrollment in to the FINRISK surveys and it was conducted following the principles of the World Medical Association's Declaration of Helsinki.

Conflict-of-interest statement: Vora P and Herrera R are employees at Integrated Evidence Generation, Bayer AG, Berlin Germany. Vora P is affiliated to Institute for Medical Information Processing, Biometry, and Epidemiology - IBE, Ludwig Maximilians Universität Munich, Munich, Germany, and Pettenkofer School of Public Health, Munich, Germany. Brobert G was an employee at Medical Affairs, Bayer AB, Solna Sweden. Salomaa V reported being an employee of the Finnish Institute for Health and Welfare, which received a funding from Bayer AG during the conduct of the study, as well as receiving honorarium for consultation from Sanofi and grants from Finnish foundation for Cardiovascular research outside the submitted work. Pietila A reported being an employee of the Finnish Institute for Health and Welfare, which received a funding from Bayer AG during the conduct of the study. Peltonen M works for the Department of Public Health and Welfare, National Institute for Health and Welfare (THL), Helsinki, Finland. Mansmann U is the director of IBE - Institute for Medical Information Processing, Biometry, and Epidemiology, Ludwig Maximilians Universität Munich, Munich, Germany.

Data sharing statement: Salomaa V and Pietila A 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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