From the Institute for Medical Information Processing,

Biometry, and Epidemiology (IBE), Munich, Germany

Dissertation
zum Erwerb des Doctor of Philosophy (Ph.D.)
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

Gastrointestinal bleedings in the general population of Finland – Occurrence and risk factors

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Jahr:

2022

Mit Genehmigung der Medizinischen Fakultät der
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List of abbreviations

BMI	Body Mass index
CI	Confidence Interval
DBP	Diastolic Blood Pressure
GIB	Gastrointestinal Bleeding
GGT	Gamma-glutamyl Transferase
HDL	High Density Lipoprotein
HR	Hazard Ratio
ICD	International Classification of Diseases
LASSO	Least Absolute Shrinkage and Selection Operator
LGIB	Lower Gastrointestinal Bleeding
NSAID	Non-Steroidal Anti-inflammatory Drugs
PIN	Personal Identification Number
SBP	Systolic Blood Pressure
SD	Standard Deviation
UGIB	Upper Gastrointestinal Bleeding
UK	United Kingdom
US	United States
VTE	Venous Thromboembolism
WHO	World Health Organization
WHR	Waist Hip Ratio

List of publications

This cumulative thesis includes following two publications:-

1. **Vora P**, Pietila A, Peltonen M, Brobert G, Salomaa V. Thirty-Year Incidence and Mortality Trends in Upper and Lower Gastrointestinal Bleeding in Finland. *JAMA Netw Open*. 2020;3(10):e2020172. [DOI:10.1001/jamanetworkopen.2020.20172]

2. Vora P, Herrera R, Pietila A, Mansmann U, Brobert G, Peltonen M, Salomaa V. Risk factors for major gastrointestinal bleeding in the general population in Finland. World J Gastroenterol 2022; 28(18): 2008-2020 [DOI: 10.3748/wjg.v28.i18.2008]

1. Your contribution to the publications

Overall, for the PhD project, I managed the collaboration contract with the Finnish Institute for Health and Welfare (THL) and became a visiting researcher to be able to visit the THL premises in Helsinki and to access and analyze data from FINRISK linked to Finnish national health registers. Together with Dr. Brobert, I obtained funding for the project.

1.1 Contribution to paper I

Supervised by Dr. Salomaa and Dr. Brobert, I conceptualized and designed the study. After creation of the analytical dataset, I performed all the programming and data management in R. I wrote the analysis plan and conducted all the analyses under the supervision of Mr. Pietila and Dr. Salomaa. All authors were involved in the interpretation of the results. Further, I drafted and revised the manuscript, and all authors were involved in the critical revision and approval of the manuscript.

1.2 Contribution to paper II

Under the supervision of Dr. Salomaa, Dr. Mansmann and Dr. Brobert, I conceptualized and designed the study. We created the analysis plan jointly together with Dr. Herrera and Prof. Mansmann. With support and supervision from Dr. Herrera and Mr. Pietila, I performed the programming, data management, and conducted the modelling and analyses in R. All authors were involved in the interpretation of the data. I drafted and revised the manuscript, and all authors critically reviewed the manuscript and provided their final approval for publication.

2. Introductory Summary

2.1 Background

Gastrointestinal bleeding

Gastrointestinal bleeding (GIB) is defined as a bleeding which occurs in any part of the gastrointestinal tract which includes esophagus, stomach, small intestine, large intestine (colon), rectum, and anus. This is further stratified into upper gastrointestinal bleeding (UGIB) and lower gastrointestinal bleeding (LGIB). UGIB includes esophagus, stomach, and duodenum; LGIB includes bleeding originating from the small bowel, colon, rectum, and anus. Upper endoscopy and colonoscopy are the commonly used diagnostic procedures to identify the site of GIB based on the symptoms. However, there can be situations when the site or the reason of GI bleeding cannot be determined and hence it is recorded as unspecified GIB. GIB remains a major burden on healthcare system with an annual incidence rate of 2.36 to 2.24 per 1000 person-years between 2001-09 and annual inpatient mortality rate of 0.07-0.05 per 1000 person-years between 1998-2006 with a case-fatality of 3% in the United States (US).[1, 2] The data from the United Kingdom (UK) and Spain show that the average number of days of hospitalization due to GIB ranges from 5 to 12 days.[3, 4] The annual treatment cost for hospitalized GIB patients in the US is estimated to be a staggering $5 billion and hospitalized UGIB patients in the UK is estimated to be £155.5 million.[5, 6]

Symptoms, causes and treatments of gastrointestinal bleeding

GIB is an acute event, which can potentially be critical and require hospitalization. It has an immediate impact at patient level and can cause pain in the stomach or chest, vomiting, tarry stool, and severe loss of blood that can lead to shock or even death. Conditions or complications that lead to GIB include peptic ulcers, varices, aneurysm, hemorrhoids, inflammation in the different parts of GI tract, ulcerative colitis, polyps, and tumors. Further, commonly known risk factors of GIB include older age, smoking, alcohol use, helicobacter pylori infection, use of medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, selective serotonin reuptake inhibitors, antiplatelets, and anticoagulants. There are specific treatments for GIB once the specific cause is determined but these treatments are often invasive and heavy and hence prevention of GIB is important. Proton pump inhibitors may be given in case of UGIB, site of the bleed can be treated with laser, or removal of polyps via colonoscopy etc. Blood transfusions might be required in case of severe loss of blood and blood thinning medications must be stopped.

Knowledge gap

Most of the studies investigating the trends and epidemiology of GIB, have focused on UGIB especially bleeds related to peptic ulcers and very few studies have reported on LGIB. There are very few studies, mainly from North America and a few European countries, investigating mainly the trends of UGIB in general population in the last two decades. Additionally, prospective follow-up data on GIBs is limited. Therefore, population based, representative data on trends and epidemiology of GIB, especially LGIB was limited.[7] Further, it is important to investigate the trends of GIB to better understand the impact of preventative interventions, public health measures, and lifestyle and environmental changes. This can further help to shape future policies for diagnosis, treatment, and management of GIB.

Non-drug related factors associated with GIB are largely unknown. Many studies have investigated factors associated with GIB, however most of the studies focused on patients taking medications that were associated to GIB or specific populations such as elderly, hospitalized patients, and patients in critical care units.[8-13] Very few studies have investigated the risk factors of GIB in general population. Additionally, most of the studies investigating risk factors of GIB lacked data on laboratory parameters, lifestyle factors, and data on physical activity, especially studies using administrative data sources. Few studies based on hospitalized patients have evaluated laboratory and clinical parameters for GIB but lack generalizability. Some studies have also investigated physical activity, smoking, alcohol consumption and related disorders.[14-16] Different studies have looked at the different risk factors separately. Therefore, to identify independent risk factors of GIB, it is important to understand the association of these additional parameters on the risk of GIB when considered together with demography and medical history. Understanding independent risk factors for GIB will support identifying patients with high risk of GIB to target preventative interventions. It would be particularly relevant for future studies investigating risk of GIB where some of these variables are lacking or not collected.

Finnish data sources

Historically in the 60s, Finland had one of the highest rates of coronary heart disease incidence and mortality. They implemented North Karelia Project to lower these rates and were extremely successful and able to decrease it by 80%. This project continued as National FINRISK surveys as part of the World Health Organization (WHO) MONICA Project and followed protocol of the WHO MONICA Project and later, the European Health Risk Monitoring Project.[17-19] These surveys were carried out every five years for over 40 years since 1972. For every cross-sectional survey, a random sample was taken from the National Population Register which was representative for five or six geographical areas of Finland with an aim to collect data on risk factors and chronic diseases and health behavior in working age population (25-74 years). The surveys enrolled at least 250 subjects of each sex and 10-year age group from each geographic area. The participation rate was >90% in 1972 survey however over time decreased to ~60% by 2012 survey. The responders to the invitation to participate were eventually recruited in the

study. The size of the cohort ranged from 6000-8000 persons per survey. Participants provided a written informed consent and the Coordinating Ethics Committee for the Helsinki and Uusimaa Hospital District Helsinki, Finland approved the study. Participants were invited for clinical examination including interviews conducted by specifically trained nurses. Participants prefilled the study questionnaires which were reviewed by the nurse during the visit. FINRISK survey collected data on socioeconomic status, chronic diseases, medical history, diet, exercise, anthropometric measures, smoking and alcohol consumption, blood pressure and laboratory parameters. The survey questionnaires have been updated over the years however the core questions have remained the same.[19]

Finland has a long tradition of maintaining health registers established as early as 1953. There are more than 21 health registers for different conditions and specialties. These electronic registers are nationwide and cover the entire population of Finland, unless they emigrate which is a very small proportion. Additionally, personal identification number (PIN) was introduced in 1964. It is given to every inhabitant (citizen or permanent residents) and remains the same throughout their life span.[20] With the help of this PIN, the records of individuals can be linked through multiple registers/datasets and can be used to create comprehensive longitudinal history through the healthcare system with minimal loss to follow-up which allows to follow individuals from birth to death. For our project, we linked the data from FINIRSK surveys to the nationwide electronic health registers which included Hospital Discharge Register, Causes of Death Register and Drug Reimbursement Register.[20]

The hospital discharge register, started in 1967, is maintained by National Institute for Health and Welfare and includes individual's PIN, main reason for hospitalization and three further diagnoses, the dates when an individual was admitted and discharged from the hospital, medical services and procedures provided in the hospital, whether as outpatient, inpatient, or emergency department setting. Filling in this information is mandatory by law and therefore it is accurately recorded in these registers.[21] The Causes of Death Register, started in 1969, is maintained by Statistics Finland, where the consistency of the underlying cause of death is checked by a specialist physician in forensic medicine and a nosologist and the diagnosis is corrected, if necessary. The Drug Reimbursement Register started in 1994 contains information on all reimbursed prescription medicines, irrespective of the setting. However, medications that are purchased over the counter and medicines administered in the hospitals are not captured by this register.[20] Through record linkage of data from FINRISK surveys to the nationwide health registers we were able to create granular dataset for the participants with detailed baseline information (as described above) and long longitudinal follow-up. The data we used for the study was pseudonymized and the use of the data was approved by the Finnish Institute for Health and Welfare in 2017.

2.2 Aims

With our first paper, we aimed to address the limited knowledge on the occurrence of major GIB in the general population of northern Europe. We stratified by type of GIB and focused

especially on LGIB. Therefore, we evaluated the incidence, recurrence, and mortality rates, as well as case fatality of UGIB and LGIB, and their trends in the general population of Finland from 1987 to 2016.

Further, as the information on risk factors of GIB in the general population was limited, especially on lifestyle factors and laboratory parameters, we focused our second paper on evaluating the risk factors of GIB in the general population of Finland.

2.3 Methods

2.3.1 Occurrence of major GIB

To evaluate the occurrence of major GIB, we incorporated data from six FINRISK survey cohorts (1987, 1992, 1997, 2002, 2007, 2012) which yielded 39,054 unique participants aged 25 to 74 years after excluding participants with a history of hospitalization for GIB at baseline. These participants of FINRISK surveys were followed up in the health registers from enrollment up to incident GIB hospitalization, death or end of follow-up which was December 31st, 2016. GIB was identified using International Classification of Diseases (ICD)-9 and ICD-10 codes listed in detail in the supplementary material in our publications. The rates were presented overall and stratified by the type of GIB, i.e., UGIB, LGIB, and unspecified GIB, and further reported by gender and age-group. Incidence rate was calculated as the number of incident GIB events divided by person time at risk. Recurrence rate was calculated as the number of second GIB events after an incident GIB divided by person time at risk. A GIB was considered recurrent if it was of the same type as the previous one and the records were at least 30 days apart. Mortality rate was calculated as the number of deaths due to GIB divided by the person time at risk. Case-fatality was calculated as the number of deaths due to GIB within 28 days of incident GIB divided by total number of participants experiencing GIB. The rates were age standardized using the 2013 standard population weights for Europe.[22] Time trends in incidence rates were calculated for every 5-year period from 1987 to 2016 for each FINRISK survey cohort.

2.3.2 Risk factors of major GIB

To evaluate the risk factors of major GIB, we used data from five FINRISK survey cohorts (1987, 1992, 1997, 2002, 2007) with 33,508 unique participants between the age of 25 to 74 years after excluding participants with history of hospitalization for GIB at baseline. Incident major GIB was GIB that required hospitalization or was the cause of death. These participants of FINRISK surveys were followed up in the electronic health registers from enrollment up to incident GIB hospitalization or death, death from any cause or maximum of ten years, whichever occurred first. GIB was identified using ICD-9 and ICD-10 codes.

Potential risk factors of GIB included data from FINRISK surveys which included demographic data such as age, gender, year or enrollment, and region; socioeconomic factors such as

marital status, occupation, education; lifestyle factors such as smoking status, alcohol consumption, coffee consumption, body mass index (BMI), waist hip ratio (WHR), physical activity; blood pressure; and laboratory parameters such as total cholesterol, high density lipoprotein cholesterol (HDL), gamma glutamyl transferase (GGT). Morbidities were obtained from the hospital discharge register, causes of death register, as well as from the drug reimbursement register and prescription register using drugs as proxies for chronic conditions. Morbidities included any type of cancer, any type of psychiatric disorder; cardiovascular diseases such as stroke, venous thromboembolism (VTE), ischaemic heart disease, valvular heart disease, atrial fibrillation, peripheral artery disease, heart failure, high blood pressure; precursors of GIB without bleeding which included gastritis, intestinal diseases, esophageal varices, esophagitis, hemorrhoids, colitis, Crohn's disease; osteoarthritis, connective tissue disorders, diabetes, chronic obstructive pulmonary disease, asthma, liver disorders and anemia.

For variable selection, we used the Cox LASSO (Least Absolute Shrinkage and Selection Operator) method which excludes covariates that are uninfluential in the model and provides an interpretable set of variables from a larger set.[23] Further Cox proportional hazards model was fitted based on the output form LASSO to obtain Hazard ratios (HR) for the risk factors of GIB with their respective 95% confidence intervals. Continuous variables were standardized by subtracting the value of the covariate from its average and dividing by its standard deviation (SD). There were less than 3% of missing values in the baseline data and those were excluded from the analyses.

2.4 Results

2.4.1 Incidence

Among the 39,054 participants, we observed 1081 individuals experiencing an incident GIB throughout the follow-up. The overall incidence rate of major GIB was 2.10 per 1000 person-years (95% Confidence Interval (CI), 1.96-2.25). After stratifying by type of GIB, the rate was higher in LGIB compared to UGIB (1.26 vs 0.94 per 1000 person-years). When each type of GIB was further stratified by gender, the rates were found to be higher in men compared to women. (see Table 1) The trends over time showed that the rates or UGIB were stable over time; however the rates of LGIB increased over time and decreased in the last decade of follow-up.

2.4.2 Recurrence

We identified 60 recurrent UGIB of the 494 incident UGIB and 49 recurrent LGIB of the 645 incident LGIB. The recurrence rate was higher in participants experiencing UGIB compared to LGIB (22.4 vs 12.3 per 1000 person-years) and when stratified by gender, it was higher in men then in women. (see Table 1). The trends over time showed constant increase for both UGIB and LGIB and in general the recurrence rate was higher for UGIB than for LGIB. Most recurrent bleeds occurred within 1-3 years after the incident GIB.

2.4.3 Mortality due to GIB

A total of 57 deaths caused (primary or secondary) by GIB, the majority of which were due to UGIB, and the lowest rate was seen for LGIB. Mortality due to GIB was highest in UGIB and lowest in LGIB (0.07 vs 0.01 per 1000 person-years). It was higher in men than in women for UGIB and unspecified GIB. Throughout the study period there were only four deaths due to LGIB. (see Table 1) We didn't have enough numbers to calculate mortality trends over time.

2.4.4 Case-Fatality due to GIB within 28 days

Of all the 57 fatalities due to GIB, 49 (86%) occurred within 28 days of the incident GIB. Case-fatality was highest for unspecified GIB compared to UGIB (8.8% vs 7.0%) and the numbers were too low for LGIB. Case fatality was higher in men than in women for UGIB and unspecified GIB. (see Table 1)

Table 1**. Age standardized incidence, recurrence, mortality, and case-fatality of GIB from 1987-2016**

	Upper GI Bleedings	Lower GI Bleedings	Unspecified GI Bleeding
	Incidence rates per 1000 person years		
Men	n=321; 1.27 (1.12-1.44)	n=371; 1.50 (1.34-1.68)	n=83; 0.33 (0.26-0.41)
Women	n=173; 0.64 (0.54-0.76)	n=274; 1.04 (0.90-1.20)	n=52; 0.21 (0.15-0.28)
Total	n=494; 0.94 (0.85-1.04)	n=645; 1.26 (1.15-1.38)	n=135; 0.26 (0.22-0.32)
	Recurrence rates per 1000 person years		
Men	n=39; 26.0 (18.4-35.7)	n=29; 13.8 (8.9-20.2)	n=16; 76.1 (34.9-136.0)
Women	n=21; 18.6 (11.0-29.2)	n=20; 11.2 (6.4-17.9)	n=10; 72.3 (27.5-144.4)
Total	n=60; 22.4 (16.9-29.0)	n=49; 12.3 (8.9-16.6)	n=26; 71.5 (40.2-113.5)
	Cause-specific mortality rates per 1000 person-years		
Men	n=30; 0.11 (0.07-0.16)	n=2; 0.006 (0.001-0.02)	n=15; 0.06 (0.03-0.11)
Women	n=8; 0.03 (0.01-0.06)	n=2; 0.014 (0.000-0.06)	n=0
Total	n=38; 0.07 (0.04-0.09)	n=4; 0.01 (0.001-0.03)	n=15; 0.03 (0.02-0.05)
	Case Fatality within 28 Days (%)		
Men	n=27; 8.8% (5.6-13.1)	n=1; 0.3% (0.004-1.6)	n=12; 16.2% (6.7-31.0)
Women	n=7; 3.5% (1.2-7.5)	n=2; 0.6% (0.05-2.1)	n=0
Total	n=34; 7.0% (4.7-10.1)	n=3; 0.4% (0.1-1.3)	n=12; 8.8% (3.9-16.2)

GI: Gastrointestinal

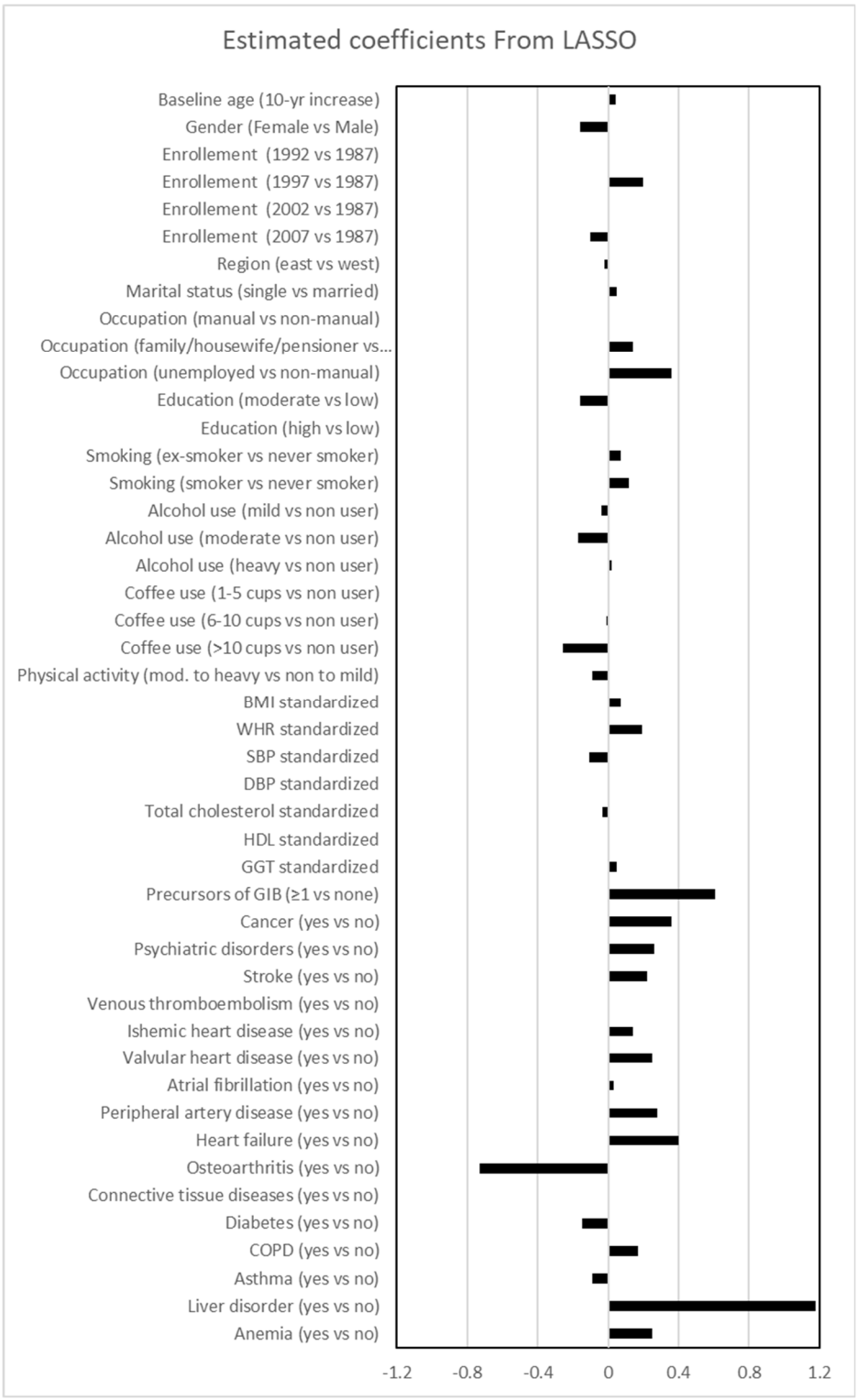
2.4.5 Risk factors of major GIB

Of the 33,508 participants, we observed 403 individuals experiencing an incident GIB within 10 years of enrollment in the FINRISK survey. Overall, the potential risk factors were proportionally higher in participants with GIB compared to participants without GIB; except high coffee consumption 6-10 cups per day (21.3% vs 27.2%), moderate to heavy physical activity (12.9%

vs 21.4%), mean HDL (1.39 mmol/L vs 1.44 mmol/L), and osteoarthritis (5.0% vs 6.2%), respectively.

LASSO with all covariates provided us the best model fit which would be between 12 to 39 covariates and excluded the non-essential ones. Estimated coefficients for covariates using LASSO suggest decreased risk of GIB if negative, increased risk if positive, and un-influential and can be removed from the model if zero. (see Figure 1) Therefore, we were able to exclude diastolic blood pressure (DBP), HDL, VTE and connective tissue diseases. However, categorical variables were kept in the model even if one of the strata had a zero coefficient.

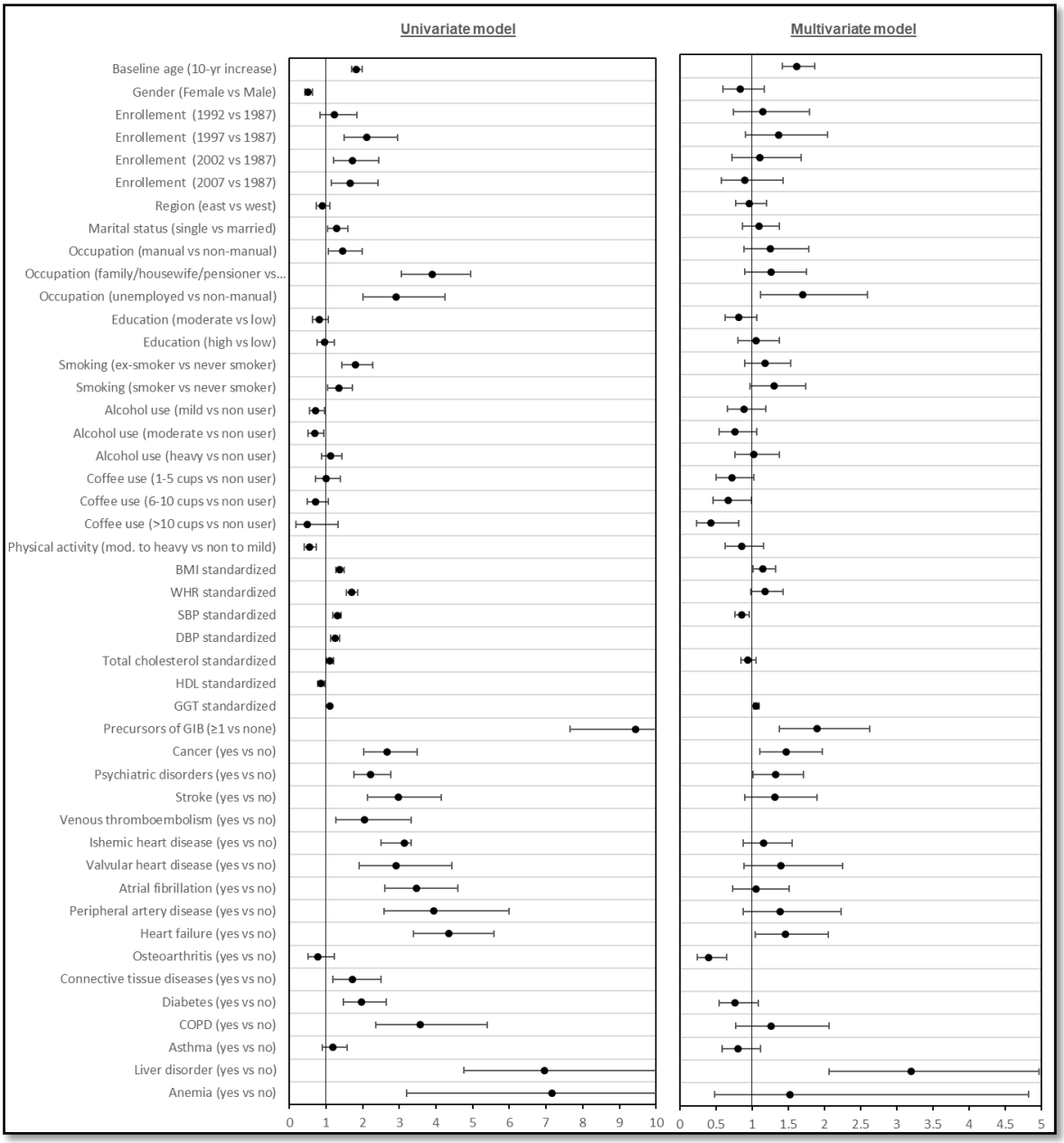
Figure 1. Estimated coefficients from LASSO using Cox regression for the risk factors of major gastrointestinal bleeding.



COPD: Chronic obstructive pulmonary disease; GGT: Gamma-glutamyl Transferase; HDL: High Density Lipoprotein; DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure; BMI: Body Mass Index; WHR: Waist Hip Ratio; Mod.: Moderate; Single: Single, separated, divorced, or widow; Married: Married, cohabiting, or registered partnership; Manual: factory, construction, farming, or forestry; Non-manual: office or studying; West: West Finland includes Turku and Loimaa as well as Helsinki and Vantaa; East: East Finland includes North Karelia, North Savo, Oulu, and Lapland; Educational tertiles (low, medium, high) were calculated according to years of education and were specific to the birth cohorts; Precursors of GIB: Includes conditions without gastrointestinal bleeding such as gastritis, intestinal diseases, esophageal varices, esophagitis, hemorrhoids, colitis, Crohn's disease.

Univariate and multivariate analyses for each potential risk factor and its association to GIB are presented in Figure 2. In our multivariate model, we found that baseline age, unemployment, increased BMI, increased GGT levels, one or more precursors of GIB, any cancer, any psychiatric disorder, heart failure, and liver disorders were all associated with an increased risk of major GIB. Further, systolic blood pressure (SBP), 6-10 cups per day of coffee or >10 cups per day of coffee, and history of osteoarthritis were associated with a decreased risk of major GIB.

Figure 2. Estimates for risk factors of major gastrointestinal bleeding using univariate and multivariate models shown as hazard ratios with 95% confidence intervals.



COPD: Chronic obstructive pulmonary disease; GGT: Gamma-glutamyl Transferase; HDL: High Density Lipoprotein; DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure; BMI: Body Mass Index; WHR: Waist Hip Ratio; Mod.: Moderate; Single: Single, separated, divorced, or widow; Married: Married, cohabiting, or registered partnership; Manual: factory, construction, farming, or forestry; Non-manual: office or studying; West: West Finland includes Turku and Loimaa as well as Helsinki and Vantaa; East: East Finland includes North Karelia, North Savo, Oulu, and Lapland;

Educational tertiles (low, medium, high) were calculated according to years of education and were specific to the birth cohorts; Precursors of GIB: Includes conditions without gastrointestinal bleeding such as gastritis, intestinal diseases, esophageal varices, esophagitis, hemorrhoids, colitis, Crohn's disease.

2.5 Discussion

Overall, our project showed that the rates of UGIB were stable over time; however the rates of LGIB showed an increase in the earlier period followed by a decrease in the later decade. Recurrence rate also showed an increasing trend; higher with UGIB than LGIB. Case-fatality was stable; however higher in men than in women. When investigating risk-factors further, apart from the known risk-factors, we identified unemployment, higher BMI, higher levels of GGT significantly associated with increased risk of GIBs, whereas high daily coffee consumption (>5 cups) as well as higher systolic blood pressure were found to be significantly associated with decreased risk of GIB. The rates of overall GIB and UGIB were similar to the other countries in Europe but lower than in the United States.[2, 24, 25] However, the rates of LGIB were higher in our study compared to the US and some European countries but showed decreasing trend similar to our study [1, 4, 26] The proportion of recurrent UGIB was similar to other studies[25] but the proportion of recurrent LGIB was lower than in other studies.[27] Case-fatality due to GIB decreased in the early years and then remained stable in the last two decades similar to studies from the US and Spain.[1, 4]

In terms of risk factors, we showed that higher coffee consumption (>5 cups a day) was associated with a decreased risk of GIB not investigated in previous studies. This is above average coffee consumption but common in Finland. Finland ranks among the world's top coffee consuming nations per capita ~10-12kg per person per year with an average of 3-5 cups per day.[28-30] In our study population, only 1.9% reported to consume >10 cups per day and 27.1% reported to consume 6-10 cups per day. Further, studies have shown a protective effect of coffee from colon cancer as well as liver diseases which are major causes of GIB.[31-34] Our analyses showed that SBP was associated with decreased risk of GIB similar to a previous study which showed a decrease in SBP associated with increased risk of GIB. Of the anthropomorphic measures and potential markers of fitness, BMI was associated to increased risk of GIB. We found that alcohol consumption and smoking were not associated with GIB; however, GGT which is a biomarker of liver function was associated to increased risk of GIB.[35] We found that unemployment was associated with increased risk of GIB. Education had no association. Our study was the first to evaluate these factors in the presence of the previously studied factors. We saw in our analyses that history of osteoarthritis was associated with decreased risk of GIB although these patients are treated with NSAIDs and corticosteroids which are associated with increased risk of GIB.[36, 37] Better management of patients with osteoarthritis and co-prescription of PPI may explain this, at least in part.[38] History of osteoarthritis was not significant in the univariate model but showed a protective effect in the multivariate model. We cannot exclude an artefact caused by complex correlations of multiple covariates among a smallish number of patients with osteoarthritis. Additionally, we cannot exclude misclassification of osteoarthritis patients in the registers because it is not a common

cause of hospitalization or death and is mainly treated at the GP level in health centers. History of cardiovascular diseases, which is a proxy for use of antiplatelets and anticoagulants,[39] was not associated with significant increased risk of GIB in our study. Overall, the risk factors that were studied have complex correlation structures which were not further evaluated.

2.6 Strengths and Limitations

The strengths of the study included the large sample size, representative of the population of Finland, minimal loss to follow-up, long-term follow-up, minimal missing data (<3%), handled multicollinearity and overfitting by using LASSO approach. Study limitations included use of health register data which were originally collected for administrative purposes and therefore potential misclassification of GIB cases; participation rate has decreased overtime. The number of deaths due to GIB were too low to estimate their trends. Covering 30 years of follow-up, includes improvements in diagnostic and coding accuracy and therefore the time-trends data should be interpreted accordingly. Due to the limited number of cases to the number of variables to be evaluated, GIB was not stratified by site of GIB. Over-the-counter medications are not recorded in the registers and hence couldn't be accounted for in the model. Some of the self-reported information such as alcohol and smoking in FINRISK surveys might be under reported. Repeated measurement after baseline were not conducted within FINRISK surveys and hence lifestyle changes could not be considered. Finally, with observational data, we are not able account for all potential confounding.

2.7 Clinical implications

These results can be used to improve care in patients experiencing GIB, target preventative interventions for individuals at risk of GIB, and serve as reference for future studies investigating GIB. We showed the effect of different life-style factors and lab parameters on the risk of GIB for which the literature is scarce which should be considered in future studies on GIB. These results would further help to improve the risk scores for GIB to identify patients at high risk of GIB. These results add to the scarce literature on the occurrence and trends of GIB especially for LGIB as well as risk factors of GIB in the general population.

2.8 Conclusions

We evaluated the occurrence and risk factors of major GIB using a large sample of participants representative of the general population in Finland. The study showed that the rate of UGIB was stable over the years, however LGIB showed an increase over the years. Recurrence and mortality were higher in UGIB even though the incidence was lower compared to LGIB. This study provides us insights in the trends of GIB over the last three decades. Further, evaluating the risk factors in this population-based cohort we identified that unemployment, BMI and GGT enzyme were all associated with increased risk of major GIB and SBP and coffee consumption

were associated with a decreased risk, besides known risk factors of major GIB. These results need to be confirmed by future epidemiological and mechanistic research.

3. Paper I

Vora P, Pietila A, Peltonen M, Brobert G, Salomaa V. Thirty-Year Incidence and Mortality Trends in Upper and Lower Gastrointestinal Bleeding in Finland. *JAMA Netw Open*. 2020;3(10):e2020172. [DOI:10.1001/jamanetworkopen.2020.20172]

JAMA Network Open

Original Investigation | Gastroenterology and Hepatology

Thirty-Year Incidence and Mortality Trends in Upper and Lower Gastrointestinal Bleeding in Finland

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Abstract

IMPORTANCE Epidemiological data on lower gastrointestinal bleeding (GIB) in the general population are sparse.

OBJECTIVE To describe the incidence, recurrence, mortality, and case fatality rates of major upper GIB and lower GIB in the general population of Finland between 1987 and 2016.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study used data from the 1987 to the 2012 cycles of the National FINRISK Study, a health examination survey that was conducted every 5 years in Finland. Survey participants were adults aged 25 to 74 years who were recruited from a population register by random sampling; those with a history of hospitalization for GIB were excluded. Participants were followed up from survey enrollment to onset of GIB that led to hospitalization, death from any cause, or study end (December 31, 2016). Follow-up was performed through linkage with national electronic health registers. Data were analyzed from February 1, 2019, to January 31, 2020.

MAIN OUTCOMES AND MEASURES Incidence, recurrence, mortality, and case fatality rates for all, upper, lower, and unspecified GIB. Outcome measures were stratified by sex and age group.

RESULTS Among the 39 054 participants included in the study, 494 (1.3%) experienced upper GIB (321 men [65.0%]; mean [SD] age, 52.8 [12.1] years) and 645 (1.7%) had lower GIB (371 men [57.5%]; mean [SD] age, 54.0 [11.7] years). The age-standardized incidence rate was 0.94 per 1000 person-years (95% CI, 0.85-1.04) for upper GIB and 1.26 per 1000 person-years (95% CI, 1.15-1.38) for lower GIB; the incidence was higher in men than in women. Between 1987 and 2016 the incidence rate of upper GIB remained mostly stable, ranging from 0.40 to 0.66 per 1000 person-years, whereas constant increases occurred in the incidence of lower GIB until the rate stabilized. The proportion of recurrent GIB events showed an increasing trend from 1987 to 2016. The upper GIB–specific mortality was higher (0.07 per 1000 person-years; 95% CI, 0.04-0.09) than the lower GIB–specific mortality (0.01 per 1000 person-years; 95% CI, 0.001-0.03). Case fatality was high for those with upper GIB (7.0%; 95% CI, 4.7-10.1) compared with those with lower GIB (0.4%; 95% CI, 0.1-1.3). Case fatality remained stable over the years but was higher in men (between 5% and 10%) than women (<2%) with GIB.

CONCLUSIONS AND RELEVANCE This study found that the overall incidence rate of upper GIB was lower than the incidence of lower GIB, but the recurrence, mortality, and 28-day case fatality were higher in participants with upper GIB. These data can serve as a reference when putting into context the rates of drug-associated GIB and can inform efforts to improve GIB care and outcome and to prevent rebleeding or death for patients with major GIB.

JAMA Network Open. 2020;3(10):e2020172. doi:10.1001/jamanetworkopen.2020.20172

Key Points

Question What are the incidence and mortality rates and trends in major upper and lower gastrointestinal bleeding (GIB) in Finland from 1987 to 2016?

Findings In this cohort study of 39 054 Finnish survey participants, the age-standardized incidence rate of major upper GIB was lower than the rate of lower GIB. Mortality rate and case fatality were higher in participants with upper GIB compared with lower GIB.

Meaning Results of this study suggest that the outcome for GIB did not seem to improve over the years and that the incidence, recurrence, and mortality data can inform efforts to improve care and prevent rebleeding or death for patients with major GIB.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Gastrointestinal bleeding (GIB) is an acute and potentially life-threatening event. Although GIB can usually be treated successfully, it represents a substantial socioeconomic burden and has a huge impact at the patient level, including hemodynamic instability, vomiting, abdominal pain, or discomfort, all of which affect daily functioning.[1] In 2006 in the United States, the hospitalization rate associated with GIB was 375 per 100 000 people and the in-hospital mortality was 5 per 100 000 people.[2] In the United Kingdom, the total annual cost of hospitalizations associated with acute upper GIB and its treatment was estimated to be approximately £155.5 million (approximately US $207.6 million).[3] Individuals at high risk of GIB include those with peptic ulcers, inflammation in the gastrointestinal tract, liver cirrhosis, or polyps or tumors in the digestive tract as well as those who use blood-thinning medications or nonsteroidal anti-inflammatory drugs.[4] Although many studies have reported the occurrence of GIB in cohorts of patients with certain prescribed medications,[5-9] most studies have focused on upper GIB. Lower GIB is common, but data on lower GIB are sparse. Few studies have examined the temporal trends of GIB in the general population, and most of the available data are limited to North America[1,2,10] and Southern Europe.[11-13] Data from the general population in the Nordic region are lacking. In conducting the present cohort study, we aimed to describe the incidence, recurrence, mortality, and case fatality rates of major upper and lower GIB in the general population of Finland between 1987 and 2016.

Methods

The National FINRISK Study surveys were approved by the ethical committee of the Finnish Institute of Health and Welfare and the Coordinating Ethical Committee of Helsinki and Uusimaa Hospital District in Finland. Informed consent for all participants was obtained at the beginning of the FINRISK surveys. Study participants were pseudonymized, and the secondary use of the survey data in the present observational prospective cohort study was approved by the Finnish Institute of Health and Welfare in 2017. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[14]

Study Design and Study Population

This cohort study used data from participants in the FINRISK health examination surveys in Finland.[15] Briefly, FINRISK, which followed the EHES (European Health Examination Survey)[16] and the MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease)[17] project protocols, was a large population-based, cross-sectional study on risk factors of chronic, noncommunicable diseases. In each survey, a random and representative sample of the population was invited from several geographic regions of Finland, and those who responded to the invitation were enrolled. Initiated in 1972, the FINRISK surveys were carried out every 5 years, with a cohort size of 6000 to 8800 per survey.[15] Participants were stratified into cohorts that contained at least 250 people of each sex and each 10-year age group from each geographical area.[15] The participation rate in the 1972 survey was approximately 90% but gradually decreased over time to approximately 50% in 2012.[15]

We included data from the 1987 to 2012 FINRISK survey cohorts. A total of 39 438 unique participants aged 25 to 74 years were enrolled in the surveys during these periods. Of these participants, 384 were excluded because they had a history of hospitalization for GIB at baseline, resulting in a cohort size of 39 054 individuals. Baseline characteristics, including age, sex, marital status, educational level, occupation, and geographical area, were ascertained at enrollment. To identify incident cases of GIB, we followed up the participants using record linkage to the nationwide electronic health registers, which included the hospital discharge register and causes of death register. These national registers cover virtually all persons living in Finland. The follow-up period was from the date of enrollment in the survey (when the health examination was conducted) to the onset

of GIB that led to hospitalization, death from any cause, or end of the follow-up period (December 31, 2016), whichever occurred first.

We further subdivided the cohort into participants with incident GIB and those without incident GIB. Cases of GIB were stratified into upper, lower, or unspecified GIB using *International Classification of Diseases, Ninth Revision* (*ICD-9*) or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes. The list of *ICD-9* and *ICD-10* codes for upper, lower, and unspecified GIB is available in eTable 1 in the Supplement. A participant could have experienced GIB at more than 1 site, and a separate follow-up was conducted for each type of GIB (upper, lower, and unspecified). Incidents of major GIB were defined as GIB that led to hospitalization or GIB-specific death and were identified from the hospital discharge register and causes of death register using *ICD-9* and *ICD-10* codes. These events were either the main or the top 3 contributing factors in hospitalization or the underlying, direct, or contributing causes of death. Gastrointestinal bleeding was considered unspecified when the location of the bleeding was not recorded or could not be identified, and therefore the *ICD-9* or *ICD-10* code used was unspecified GIB. Recurrent GIB was identified from incident GIB until death or the end of the follow-up period, and the diagnoses had to be more than 30 days apart. The recurring GIB had to be of the same type as the incident GIB; that is, the event was considered recurrent if an individual with incident upper GIB experienced another upper GIB, if an individual with incident lower GIB experienced another lower GIB, or if an individual with incident unspecified GIB experienced any other type of GIB at any site.

Statistical Analysis

We calculated incidence rates, recurrence rates, and GIB-specific mortality rates of all GIB, upper GIB, lower GIB, and unspecified GIB as the number of events divided by the person-time at risk. Case fatality was calculated as the number of deaths from GIB within 28 days of experiencing a GIB event divided by the number of individuals with incident GIB during the follow-up. Baseline age was used to calculate the person-time at risk and to stratify participants into different age groups (eg, 24-29, 30-39, 40-49 years and so on) to ascertain the age-specific rates. Age standardization was conducted using the European standard population weights.[18] Incidence and mortality rates were reported per 1000 person-years, and case fatality was reported as a percentage. These outcome measures were further stratified by participant sex, age group (when possible), and GIB type (upper, lower, or unspecified).

The 95% CIs for rates were calculated using the Byar method for 10 or more events and the exact method for fewer than 10 events, and for proportions were calculated using the Wilson Score method.[19-21] Time trends in incidence rates were calculated for every 5-year period of the FINRISK surveys from 1987 to 2012 (ie, 1987-1991, 1992-1996, 1997-2001, 2002-2006, 2007-2011, and 2012-2016), and these survey cohorts were followed up from enrollment to the fifth year of the study period. Time trends in recurrence rate were calculated as the number of recurrent GIB events divided by the total number of GIB events within each of the 5-year periods from 1987 to 2016. Time trends in case fatality were calculated as the proportions for each of the 5-year periods from 1987 to 2016. The difference in the absolute numbers between upper GIB and lower GIB was calculated for each of the 5-year periods from 1987 to 2016.

All statistical calculations and plots were done with R, version 3.6.1 (R Foundation for Statistical Computing). Data were analyzed from February 1, 2019, to January 31, 2020.

Results

Study Population and Characteristics

The study included 39 054 participants, who contributed 627 516 person-years of follow-up for a median duration of 14.9 years. Of these participants, 1081 (2.8%) experienced a major GIB event, with 494 (1.3%) having upper GIB, 645 (1.7%) having lower GIB, and 135 (0.3%) having unspecified GIB, whereas 37 973 individuals (97.2%) did not experience GIB. The mean (SD) baseline age was

53.4 (11.9) years for all participants with incident GIB cases and 47.2 (13.2) years for those with no GIB. The participants with lower GIB and unspecified GIB were slightly older (mean [SD] age, 54.0 [11.7] years and 54.9 [11.0] years) than those experiencing upper GIB (52.8 [12.1] years), but all GIB groups were composed predominantly of male participants (upper: 65.0% men [n = 321]; lower: 57.5% [n = (371]; unspecified: 61.5% [n = 83]). The proportion of men among the participants experiencing GIB was 59.9% (n = 648) and among those without GIB was 47.5% (n = 18 026), whereas the proportions of women were 40.1% (n = 433) and 52.5% (n = 19 947), respectively. The baseline characteristics of participants are presented in eTable 2 in the Supplement.

Incidence of Major GIB

During the entire study period (1987-2016), the overall crude incidence rate of GIB was 1.74 per 1000 person-years (95% CI, 1.64-1.85) and the overall age-standardized rate was 2.10 per 1000 person-years (95% CI, 1.96-2.25). When stratified by sex, the overall age-standardized rate was higher in men than in women (2.62 per 1000 person-years [95% CI, 2.40-2.86] vs 1.62 per 1000 person-years [95% CI, 1.45-1.81]). Furthermore, when stratified by the site of GIB, the incidence rate was highest for participants with lower GIB (1.26 per 1000 person-years; 95% CI, 1.15-1.38), followed by those with upper GIB (0.94 per 1000 person-years; 95% CI, 0.85-1.04) and those with unspecified GIB (0.26 per 1000 person-years; 95% CI, 0.22-0.32). The age-standardized rates for upper GIB and lower GIB were higher in men (upper: 1.27 per 1000 person-years [95% CI, 1.12-1.44]; lower: 1.50 per 1000 person-years [95% CI, 1.34-1.68]) than in women (upper: 0.64 per 1000 person-years [95% CI, 0.54-0.76]; lower: 1.04 per 1000 person-years [95% CI, 0.90-1.20]). For unspecified GIB, no difference was observed between the sexes (men: 0.33 per 1000 person-years [95% CI, 0.26-0.41] vs women: 0.21 per 1000 person-years [95% CI, 0.15-0.28]) (**Table 1**).

Table 1. Incidence Rates of Gastrointestinal Bleeding per 1000 Person-Years Between 1987 and 2016

Variable	Upper GIB			Lower GIB			Unspecified GIB		
	No. of cases	Person-years	Incidence rate (95% CI)	No. of cases	Person-years	Incidence rate (95% CI)	No. of cases	Person-years	Incidence rate (95% CI)
Men									
Overall crude rate	321	290 385.05	1.11 (0.99-1.23)	371	289 976.25	1.28 (1.15-1.42)	83	291 719.25	0.28 (0.23-0.35)
Age-standardized rate	NA	NA	1.27 (1.12-1.44)	NA	NA	1.50 (1.34-1.68)	NA	NA	0.33 (0.26-0.41)
Age-specific rate									
24-29 y	18	36 649.38	0.49 (0.29-0.78)	13	36 668.43	0.35 (0.19-0.61)	2	36 754.04	0.05 (0.01-0.20)
30-39 y	40	69 205.99	0.58 (0.41-0.79)	38	69 250.23	0.55 (0.39-0.75)	5	69 459.11	0.07 (0.02-0.17)
40-49 y	68	72 365.87	0.94 (0.73-1.19)	79	72 134.78	1.10 (0.87-1.36)	15	72 662.50	0.21 (0.12-0.34)
50-59 y	97	65 343.17	1.48 (1.20-1.81)	119	65 258.41	1.82 (1.51-2.18)	34	65 706.76	0.52 (0.36-0.72)
60-69 y	75	39 129.32	1.92 (1.51-2.40)	94	38 974.14	2.41 (1.95-2.95)	22	39 366.73	0.56 (0.35-0.85)
70-74 y[a]	23	7691.90	2.99 (1.89-4.49)	28	7690.26	3.64 (2.42-5.26)	5	7770.16	0.64 (0.21-1.50)
Women									
Overall crude rate	173	334 257.16	0.52 (0.44-0.60)	274	333 797.99	0.82 (0.73-0.92)	52	335 252.34	0.16 (0.12-0.20)
Age-standardized rate	NA	NA	0.64 (0.54-0.76)	NA	NA	1.04 (0.90-1.20)	NA	NA	0.21 (0.15-0.28)
Age-specific rate									
24-29 y	9	46 464.70	0.19 (0.09-0.37)	11	46 438.67	0.24 (0.12-0.42)	1	46 525.64	0.02 (0.001-0.12)
30-39 y	19	81 689.35	0.23 (0.14-0.36)	24	81 674.01	0.29 (0.19-0.44)	6	81 814.23	0.07 (0.03-0.16)
40-49 y	35	81 552.84	0.43 (0.30-0.60)	50	81 514.08	0.61 (0.46-0.81)	13	81 798.41	0.16 (0.08-0.27)
50-59 y	52	75 957.69	0.68 (0.51-0.90)	96	75 695.07	1.27 (1.03-1.55)	12	76 252.48	0.16 (0.08-0.27)
60-69 y	46	41 490.36	1.11 (0.81-1.48)	71	41 380.43	1.72 (1.34-2.16)	15	41 720.87	0.36 (0.20-0.59)
70-74 y[a]	12	7102.26	1.69 (0.87-2.95)	22	7095.74	3.10 (1.94-4.69)	5	7140.73	0.70 (0.23-1.63)
Total									
Crude rate	494	624 642.87	0.79 (0.72-0.86)	645	623 774.23	1.03 (0.96-1.12)	135	626 971.69	0.22 (0.18-0.26)
Age-standardized	NA	NA	0.94 (0.85-1.04)	NA	NA	1.26 (1.15-1.38)	NA	NA	0.26 (0.22-0.32)

Abbreviations: GIB, gastrointestinal bleeding; NA, not applicable.

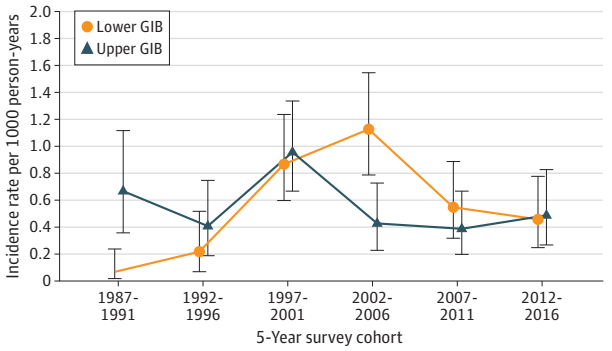
[a] Recruitment of FINRISK survey participants aged 70 to 74 years mainly started in 1997.

We found that a total of 102 upper GIB events and 108 lower GIB events occurred in the study participants after restricting each FINRISK cohort (1987-2012) from enrollment to 5 years of follow-up to obtain incidence rates for each of the 5-year periods from 1987 to 2016. Trends over the years showed that the incidence of upper GIB remained stable over the past 30 years between 0.40 and 0.66 per 1000 person-years, except for a slight increase to 0.95 per 1000 person-years that occurred in the 1997 to 2001 period (**Figure 1**). For lower GIB, the incidence constantly increased from 0.06 per 1000 person-years in the 1987 to 1991 period to 1.12 per 1000 person-years in the 2002 to 2006 period. Since then, the incidence rate of lower GIB has decreased by almost half (0.54 per 1000 person-years), has become stable in the past decade, and is similar to the upper GIB incidence rate (0.45 per 1000 person years; 95% CI, 0.24-0.77) (Figure 1). The difference in the absolute number of events between upper GIB and lower GIB was that the number of upper GIB events was higher than lower GIB (118 vs 92) until the 1997 to 2001 period. Since then, the number of lower GIB events has increased substantially and remained high until the end of follow-up on December 31, 2016 (eFigure in the Supplement).

Recurrence of Major GIB

We found a total of 60 recurrent upper GIB events in patients with an incident upper GIB, 49 recurrent lower GIB events in patients with an incident lower GIB, and 26 recurrent GIB events in patients with an incident unspecified GIB. The estimated recurrence rate of unspecified GIB was the highest (71.5 per 1000 person-years; 95% CI, 40.2-113.5), but the absolute number of cases was low (n = 26). The recurrence rate for upper GIB was higher (22.4 per 1000 person-years; 95% CI,

Figure 1. Incidence Rate Trends in Major Upper and Lower Gastrointestinal Bleeding (GIB) for 5-Year Cohorts



Error bars indicate 95% CIs.

Table 2. Recurrence Rates of Gastrointestinal Bleeding per 1000 Person-Years Between 1987 and 2016

Variable	Incident upper GIB			Incident lower GIB			Incident unspecified GIB		
	No. of cases	Person-years	Recurrence rate (95% CI)	No. of cases	Person-years	Recurrence rate (95% CI)	No. of cases	Person-years	Recurrence rate of any GIB (95% CI)
Men									
Overall crude rate	39	1460.0	26.7 (19.0-36.5)	29	1918.7	15.1 (10.1-21.7)	16	244.1	65.6 (37.5-106.5)
Age-standardized rate	NA	NA	26.0 (18.4-35.7)	NA	NA	13.8 (8.9-20.2)	NA	NA	76.1 (34.9-136.0)
Women									
Overall crude rate	21	1125.8	18.7 (11.5-28.5)	20	1573.0	12.7 (7.8-19.6)	10	191.6	52.2 (25.0-96.0)
Age-standardized rate	NA	NA	18.6 (11.0-29.2)	NA	NA	11.2 (6.4-17.9)	NA	NA	72.3 (27.5-144.4)
Total									
Crude rate	60	2585.7	23.2 (17.7-29.9)	49	3491.7	14.0 (10.4-18.6)	26	435.7	59.7 (39.0-87.4)
Age-standardized rate	NA	NA	22.4 (16.9-29.0)	NA	NA	12.3 (8.9-16.6)	NA	NA	71.5 (40.2-113.5)

Abbreviations: GIB, gastrointestinal bleeding; NA, not applicable.

16.9-29.0) than the recurrence rate for lower GIB (12.3 per 1000 person-years; 95% CI, 8.9-16.6). When stratified by sex, the recurrence rate for upper GIB was higher in men than in women, and no difference in recurrence rate was observed for lower GIB (**Table 2**). The proportions of recurrent events calculated over the 5-year survey cohorts from 1987 to 2012 tended to increase over time (**Figure 2**). After an incident upper GIB, 73.3% of recurrent upper GIB events (n = 44 of 60) occurred within 1 year and 88.3% of recurrent upper GIB events (n = 53 of 60) took place within 3 years, with a median (interquartile range [IQR]) follow-up of 3 (1-16) months. After an incident lower GIB event, 79.6% of recurrent lower GIB events (n = 39 of 49) occurred within 1 year and 91.8% of recurrent lower GIB events (n = 45 of 49) occurred within 3 years, with a median (IQR) follow-up of 2.5 (1-6) months.

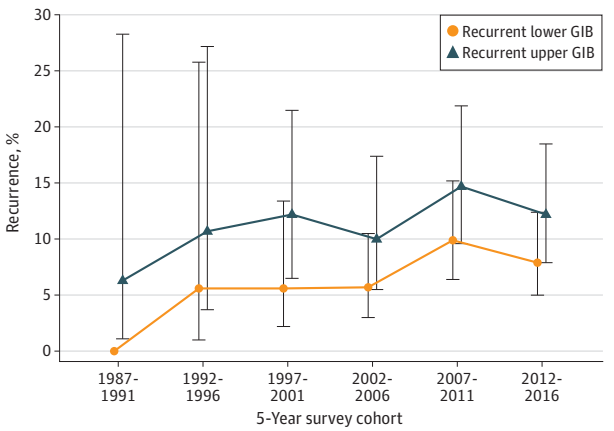
GIB-Specific Mortality and 28-Day Case Fatality

We observed 57 deaths associated with GIB during the entire study period, of which 38 (66.7%) were attributed to upper GIB, 4 (7.0%) attributed to lower GIB, and 15 (26.3%) attributed to unspecified GIB. The overall age-standardized GIB-specific mortality rate was 0.11 per 1000 person-years (95% CI, 0.08-0.14), 0.18 per 1000 person-years (95% CI, 0.13-0.24) in men, and 0.04 per 1000 person-years (95% CI, 0.02-0.08) in women. The upper GIB–specific mortality rate was 0.07 per 1000 person-years (95% CI, 0.04-0.09), the lower GIB–specific mortality rate was 0.01 per 1000 person-years (95% CI, 0.001-0.03), and the unspecified GIB–specific mortality rate was 0.03 per 1000 person-years (95% CI, 0.02-0.05). Upper GIB–specific mortality rates were higher in men than in women (0.11 per 1000 person-years [95% CI, 0.07-0.16] vs 0.03 per 1000 person-years [95% CI, 0.04-0.09]) (eTable 3 in the Supplement).

After restricting the follow-up to 5 years, we found a total of 13 GIB-specific deaths of participants. A maximum of 1 to 3 deaths occurred in each of the 5-year periods from 1987 to 2016. The numbers were too low to enable us to calculate reliable estimates for trends over time.

Forty-nine of the 57 total deaths (86.0%) occurred within 28 days of GIB diagnosis; of these 49 deaths, 34 were from upper GIB, 3 were from lower GIB, and 12 were from unspecified GIB. The overall age-standardized case fatality during the study period was 4.7% (95% CI, 3.3-6.3). When stratified by sex, the case fatality was 6.5% (95% CI, 4.5-9.0) in men and 1.8% (95% CI, 0.7-3.6) in women. The age-standardized case fatality was 7.0% (95% CI, 4.7-10.1) in participants with upper GIB, 0.4% (95% CI, 0.1-1.3) in participants with lower GIB, and 8.8% (95% CI, 3.9-16.2) in participants with unspecified GIB (eTable 3 in the Supplement).

Figure 2. Recurrent Major Upper and Lower Gastrointestinal Bleeding (GIB) for 5-Year Cohorts



Error bars indicate 95% CIs.

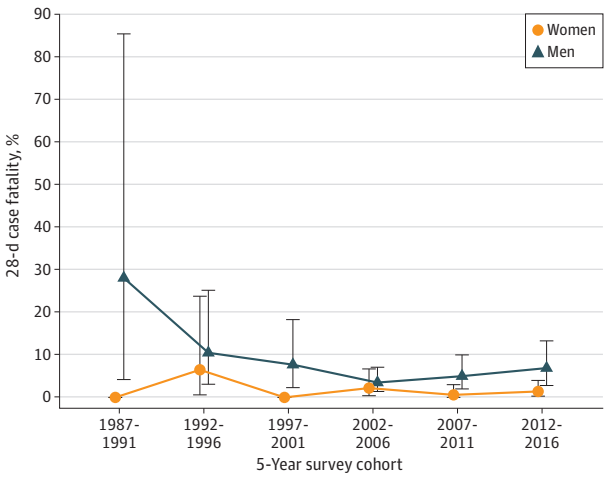
Trends in case fatality for overall GIB among men showed an initial decrease but have remained constant between 5% and 10%. For women, this case fatality trend was less than 2% in the past 2 decades (**Figure 3**). The limited number of events did not permit us to perform meaningful analyses of case fatality stratified by type of GIB.

Discussion

This population-based cohort study from Finland found that the incidence rate of lower GIB was substantially higher than that of upper GIB, and incidence of upper GIB has remained stable over the past 30 years. With eradication of *Helicobacter pylori*, the rate of peptic ulcer bleeding has decreased. However, upper GIB associated with *H pylori* composes approximately 15% to 20% of all upper GIB events; therefore, eradication of *H pylori* would not substantially alter the trends of overall upper GIB, which might have been counterbalanced by non-*H pylori*–associated upper GIB and other risk factors over the study period.[22] We observed a substantial increase in the incidence of lower GIB until 2006, which decreased by almost half and then stabilized in the past decade. This trend coincided with a slight increase in the incidence of colorectal cancer between 1987 and 2016, which was higher in men than women.[23] Overall, the recurrence rate of upper GIB was twice as high as the recurrence rate of lower GIB and slightly increased over the years. Further research into the potential factors associated with the increasing trends is required. Case fatality from GIB remained stable during most of the follow-up period, with higher case fatality in men than in women. Overall, the incidence and fatality associated with GIB improved from the earlier FINRISK survey periods that we analyzed. In the later surveys, however, these rates became stable, and no further improvement was observed.

A recent study in New Zealand that analyzed data from 2002 to 2015 of a population with predominantly European ancestry reported that the incidence rate of nonfatal GIB was 2.19 per 1000 person-years, which was similar to findings in the present study.[24] A review of studies from Europe on acute upper GIB that used data from the 1990s reported that the incidence rate of acute upper GIB ranged from 0.36 to 1.72 per 1000 person-years,[13] which was within or higher than the range shown in the present study. Compared with the present study, the incidence rates of upper GIB in the United States (from 1998 to 2006) were higher at between 1.46 and 1.70 per 1000 person-years and were comparable to those of Spain (from 1996 to 2005), which ranged from 0.47 to 0.87 per 1000 person-years.[2,12] Furthermore, similar to the present study, these studies showed decreased or stable incidence of upper GIB over the years, a higher incidence in men than in women, and increased

Figure 3. Twenty-Eight-Day Case Fatality Trends in Major Gastrointestinal Bleeding for 5-Year Cohorts



Error bars indicate 95% CIs.

incidence with age.[2,11-13,25,26] Few studies that reported the incidence of lower GIB in the general population showed that the rates in the United States (1998-2006), Spain (1996-2005), and Italy (2001-2010) were about half of the rate reported in our study.[10-12] Similar to this study, previous studies[10-12] reported a slight increasing trend in the incidence of lower GIB or complications. Unlike other studies, the present study showed that the incidence of lower GIB was significantly higher in men than in women.[10-12]

The proportion of recurrent upper GIB in the present study was within the range of a previous review (between 7% and 16%).[13] Another review (1994-2003) on lower GIB reported that the recurrent lower GIB ranged from 10% to 40%, which was higher than observed in this study.[27] The study from Spain reported that the mortality rates of GIB decreased over time, and several studies in the United States also reported decreasing mortality for upper GIB.[10,12,28,29] However, this trend could not be calculated in this study because of the low number of cases. Overall mortality rates of lower GIB were lower in the present study than in the review of studies in 2005.[27] Improved health care and early detection or diagnosis of bleeding are likely to be associated with the decreased mortality of GIB.[28,29] Compared with the study from New Zealand,[24] the 28-day case fatality for overall GIB was 2 times higher in our study. In addition, the trend in case fatality of GIB decreased sharply in the early years of the FINRISK surveys and remained stable in recent decades, and the case fatality range was similar to the ranges in the studies from Spain and the United States.[10,12]

We believe that the findings of this study will be useful in clinical practice. Specifically, the data can inform efforts to improve the care and outcomes for patients with GIB, especially lower GIB, and to prevent recurrent bleeding or death in patients with upper GIB. Incidence, recurrence, mortality, and case fatality rates of GIB in the general population are useful to know when putting into context the rates of drug-associated GIB.

Strengths and Limitations

This study has some strengths. It had a population-based design, a large sample size that was representative of the general population in Finland, and minimal or no participant loss to follow-up. The long-term follow-up of 30 years enabled the analysis of temporal trends of GIB over the past 3 decades, which covered changes in both characteristics of the general population and medical practice. Studies of the trends of GIB in the general population in Europe and in Asia are needed, especially for lower GIB for which research data are sparse. Upper GIB has been extensively studied, but the data on trends in the general populations of Asia and Europe may be limited and warrant further investigation. In addition, the risk factors associated with the changes in trends need to be ascertained to identify the areas for improvement.

This study also has some limitations. The electronic health register data were originally collected for administrative purposes. Accordingly, some misclassification in recording the GIB diagnoses and causes of death may have occurred; however, the magnitude of such errors is likely to be small compared with the large number of events. The number of deaths from GIB was low, and therefore the mortality and case fatality estimates had wide CIs. Diagnostic accuracy and coding accuracy have improved over time. Therefore, the time trends, especially the early rates, must be interpreted with caution. Participation in the FINRISK surveys declined over the years, and the nonparticipants were more likely to be young, to be male, to have lower socioeconomic status, and to have more chronic illnesses, which could lead to the underrepresentation of this group, especially in later surveys.[30] Recruitment of FINRISK survey participants aged 70 to 74 years mainly started in a few geographic areas in 1997, and hence the rates for this age group should be interpreted with caution.

Conclusions

This study analyzed the epidemiological data of major upper and lower GIB in a large representative sample of the general population in Finland. The incidence of upper GIB remained stable, whereas the incidence of lower GIB showed an increase over the years. Even though the overall incidence rate

of upper GIB was lower than that of lower GIB, the recurrence and mortality rates were higher in participants with upper GIB. The case fatality of all GIB remained stable in the past 2 decades. Thus, the outcomes did not seem to have improved despite more accurate diagnostic methods and likely earlier detection. The data presented here can serve as a reference for improving the care and outcome for patients with major GIB and for preventing rebleeding or death in these patients.

ARTICLE INFORMATION

Accepted for Publication: July 30, 2020.

Published: October 9, 2020. doi:10.1001/jamanetworkopen.2020.20172

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Author Contributions: Dr Salomaa and Mr Pietila had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Vora, Brobert, Salomaa.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Vora, Brobert.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Vora, Pietila, Peltonen, Brobert.

Obtained funding: Vora, Brobert, Salomaa.

Administrative, technical, or material support: Brobert, Salomaa.

Supervision: Brobert, Salomaa.

Conflict of Interest Disclosures: Mr Vora reported being an employee of Bayer AG. Mr Pietila reported being an employee of the Finnish Institute for Health and Welfare, which received a grant from Bayer AG during the conduct of the study. Dr Peltonen reported being an employee of the Finnish Institute for Health and Welfare. Dr Brobert reported being an employee of Bayer AB. Dr Salomaa reported being an employee of the Finnish Institute for Health and Welfare, which received a grant from Bayer AG during the conduct of the study, as well as receiving personal fees from Novo Nordisk and honorarium for consultation from Sanofi outside the submitted work. No other disclosures were reported.

Funding/Support: This study was funded in part by Bayer AG. Dr Salomaa was supported by the Finnish Foundation for Cardiovascular Research.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: The preliminary results of this study were presented as 2 posters at the 27th United European Gastroenterology Week Congress, October 21 and 22, 2019, Barcelona, Spain.

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SUPPLEMENT.

eTable 1. List of ICD 9 and ICD 10 Codes for Gastrointestinal Bleedings
eTable 2. Baseline Characteristics of the Study Participants by Type of Gastrointestinal Bleeding During Follow-up
eFigure. Absolute Difference Between the Number of Upper and Lower Gastrointestinal Bleeding Events for Five-Year Period Each
eTable 3. Mortality Rates and 28-Day Case-Fatality Due to Gastrointestinal Bleedings Between 1987 and 2016

4. Paper II

Vora P, Herrera R, Pietila A, Mansmann U, Brobert G, Peltonen M, Salomaa V. Risk factors for major gastrointestinal bleeding in the general population in Finland. World J Gastroenterol 2022; 28(18): 2008-2020 [DOI: 10.3748/wjg.v28.i18.2008]

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2022 May 14; 28(18): 2008-2020

DOI: 10.3748/wjg.v28.i18.2008

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Study

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

Pareen Vora, Ronald Herrera, Arto Pietila, Ulrich Mansmann, Gunnar Brobert, Markku Peltonen, Veikko Salomaa

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gaman MA, Romania; Govindarajan KK, India

Received: November 14, 2021
Peer-review started: November 14, 2021
First decision: January 9, 2022
Revised: January 22, 2022
Accepted: March 26, 2022
Article in press: March 26, 2022
Published online: May 14, 2022

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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.

Citation: Vora P, Herrera R, Pietila A, Mansmann U, Brobert G, Peltonen M, Salomaa V. Risk factors for major gastrointestinal bleeding in the general population in Finland. *World J Gastroenterol* 2022; 28(18): 2008-2020
URL: https://www.wjgnet.com/1007-9327/full/v28/i18/2008.htm
DOI: https://dx.doi.org/10.3748/wjg.v28.i18.2008

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.

Supported by Bayer AG.

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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S-Editor: Wu YXJ
L-Editor: Filipodia

P-Editor: Wu YXJ

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6. Acknowledgements

I would like to dedicate my thesis to late Prof. Dr. Joerg Hasford who unfortunately passed away during the course of my PhD. I extend my deepest condolences to his family. He was always supportive of my work and showed me the path to move forward for my doctoral research.

I am extremely thankful to have had Prof. Dr. Ulrich Mansmann as my supervisor. He has always been supportive and encouraging. Even during the times when I had doubts and uncertainty, he was confident that I would be able to overcome it and finish everything in time. This really helped to boost my confidence and reassured me that I am moving forward in the right direction. I really appreciated that with his busy schedule, he made time for me whenever I had questions and was always there for me. Both Prof. Dr. Ulrich Mansmann and Prof. Dr. Joerg Hasford were so kind and happily accepted to supervise me when I reached out to them without any hesitation. This was a great boost for me and gave a kickstart to my PhD.

I would like to extend my deepest gratitude and thanks to Prof. Dr. Veikko Salomaa for his excellent supervision. He embraced me for my doctoral research and supported me in every possible way. He ensured that all the logistics for my visits as a researcher were in place at THL in Helsinki. He always ensured that my thesis was on track and always gave me pragmatic feedback.

Dr. Gunnar Brobert has been my supervisor since I started my professional journey as an epidemiologist from my MSc to my PhD. He has shaped my career, myself as a person, and as a researcher with his values over the last 10 years. He has been an excellent mentor and hope that he is proud to see me grow over the last decade as an epidemiologist. I will always remember his words regarding medical research, “Every time we publish our research, we slightly shift the needle of knowledge towards improving care for patients in clinical practice. And even after we pass away our names would remain alive forever through our research & publications and keep making difference.” This has always been the words that has motivated me for my PhD since the beginning. He has been elemental in identifying the topic, data sources, and collaboration and has been a pillar in setting up the research topic.

Dr. Montse Soriano Gabarro, head of Epidemiology at Bayer was supportive in my development and pushed me to go higher. I would really like to thank her for giving me the opportunity in her department to start my professional career as an epidemiologist, which has completely transformed my life both personally and professionally. She was the first to propose the idea to do a PhD and not to stop with MSc. She ensured that I had all the resources to smoothly continue the research for my PhD while working full time.

I would like to thank Arto Pietila who gave me all the support I required for data management, programming, and analyses. He ensured all the logistics and my onboarding at THL in Helsinki.

I thank Dr. Ronald Herrera to guide me throughout my doctoral studies and helping with all my questions. He played an extremely important part in many aspects of my research, which was crucial for completion of my Doctoral thesis.

I’d liked to thank Dr. Kiliana Suzart-Woischnik for supporting me throughout my PhD and my career with opportunities, positivity, and enthusiasm.

I would like to thank Susan Bromley who kept me motivated throughout my PhD and always encouraged me.

I am thankful to all the colleagues at THL, Department of Public Health and Welfare who made me feel part of their team and invited me for all their activities.

I would like to extend special thanks to Tarja, Agnieszka, and our colleagues at Bayer Finland who always welcomed me whenever I visited Helsinki, their excitement and interest in my research. They made me feel at home and invited me to various extra activities.

With all my time in Finland with all the excellent colleagues both at THL and Bayer Finland I learnt a lot about Finnish culture as well as a bit of Finnish language which I always cherish. This was very refreshing and gave me the best environment for my doctoral research.

I am extremely thankful to Dr. Magda Radermacher, Monika Darchinger, and Dr. Annette Hartmann for their support at every step of the PhD program and being flexible as well as helping us with all our needs.

I would like to thank my parents for showing me the importance of knowledge and higher education, for constantly supporting me, for teaching me important life values, for giving me the freedom to choose my journey, and for all the unconditional love.

All the kind contributions were like drops of water that filled my ocean of PhD with success and I would like to thank each one of them from the bottom of my heart.

Danke Schön, Kiitos, and Thank you!!

8. Scientific Publications

1. **Vora P**, Morgan Stewart H, Russell B, Asiimwe A, Brobert G. Time Trends and Treatment Pathways in Prescribing Individual Oral Anticoagulants in Patients with Nonvalvular Atrial Fibrillation: An Observational Study of More than Three Million Patients from Europe and the United States. *Int J Clin Prac. 2022*, https://doi.org/10.1155/2022/6707985 [https://www.hindawi.com/journals/ijclp/2022/6707985/]
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