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Infectious Diseases

Associations of obesity and lifestyle with the risk and mortality of bloodstream infection in a general population: a 15-year follow-up of 64 027 individuals in the HUNT Study

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Abstract

Background: Bloodstream infections (BSI) cause considerable morbidity and mortality, and primary prevention should be a priority. Lifestyle factors are of particular interest since they represent a modifiable target.

Methods: We conducted a prospective cohort study among participants in the population-based Norwegian HUNT2 Survey, where 64 027 participants were followed from 1995–97 through 2011 by linkage to prospectively recorded information on BSI at local and regional hospitals. The exposures were: baseline body mass index (BMI) measurements; and self-reported smoking habits, leisure time physical activity and alcohol intake. The outcomes were hazard ratios (HR) of BSI and BSI mortality.

Results: During 810 453 person-years and median follow-up of 14.8 years, 1844 (2.9%) participants experienced at least one BSI and 396 (0.62%) died from BSI. Compared with normal weight participants (BMI 18.5–24.9 kg/m^2), the age- and sex-adjusted risk of a

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first-time BSI was 31% [95% confidence interval (CI) 14–51%] higher at BMI 30.0–34.9 kg/m^2, 87% (95% CI 50–135%) higher at BMI 35.0–39.9 kg/m^2 and 210% (95% CI 117–341%) higher at BMI $\geq$ 40.0 kg/m^2. The risk of BSI mortality was similarly increased. Compared with never-smokers, current smokers had 51% (95% CI 34–70%) and 75% (95% CI 34–129%) higher risks of BSI and BSI mortality, respectively. Physically inactive participants had 71% (95% CI 42–107%) and 108% (95% CI 37–216%) higher risks of BSI and BSI mortality, respectively, compared with the most physically active.

Conclusions: Obesity, smoking and physical inactivity carry increased risk of BSI and BSI mortality.

Key words: Bacteraemia, sepsis, obesity, smoking, exercise, alcohol drinking

Key Messages

- Primary prevention of bloodstream infections should be a priority for reducing their morbidity and mortality. Lifestyle factors are modifiable, and may represent an efficient target.
- Few studies have assessed infection-related mortality at the population level, or the role of multiple lifestyle factors.
- In this population-based study, we found strong dose-response relationships between obesity and the risk of BSI and BSI mortality, and the importance of obesity as a risk factor varied by infecting organism.
- Smoking was associated with increased risk of BSI and BSI mortality, even with pathogens that do not primarily infect the airways, such as *Staphylococcus aureus* and *Escherichia coli.*
- The combined effects of obesity, smoking and physical inactivity increased the risk of BSI and BSI mortality 5- to 6-fold at the population level.

Introduction

Bloodstream infection (BSI), defined as bacteraemia associated with infection, is a cause of considerable morbidity and mortality.[1] The overall incidence is approximately 180/100 000 person-years in high-income countries and, with mortality rates of 20-30/100 000 person-years, it ranks among the top seven causes of death in North America and parts of Europe.[2]

In recent years there have been increased initiatives to identify risk factors for BSI, sepsis and other severe bacterial infections.[3–6] Lifestyle factors are of particular interest since they are modifiable, and optimization could reduce the burden of BSI at the population level. Yet, the influence of lifestyle factors on the occurrence of severe infections is insufficiently known. Studies assessing the role of lifestyle factors in the risk of infection have usually focused on specific infections or microorganisms.[7–10] Few studies have assessed either infection-related mortality at the population level or the role of multiple lifestyle factors. In this Norwegian population-based cohort study of 64 027 subjects, we assessed the associations of obesity, smoking, physical inactivity and alcohol intake with the risk of BSI and BSI mortality.

Methods

Nord-Trøndelag county in central Norway has a population of approximately 130 000. The county consists of rural areas and small towns. The county is considered generally representative of Norway with regard to sources of income, age distribution, morbidity and mortality, but the average income and prevalence of higher education and current smoking are a little lower than the Norwegian average, and the county has no large cities.[11] The HUNT Study (an acronym for the Nord-Trøndelag Health Study, in Norwegian: Helseundersøkelsen i Nord-Trøndelag) is a series of surveys in which all inhabitants in Nord-Trøndelag aged 20 years or older were invited to participate: HUNT1 (1984–86), HUNT2 (1995–97) and HUNT3 (2006–08).[12] The present study was performed among all participants of HUNT2, where 93 865 persons were invited and 65 236 (69.5%) participated. Among them, 47 316 (72.5%) had also participated in HUNT1.[12] The participants returned questionnaires covering a wide range of health-related topics including lifestyle factors and previous illnesses. They attended a clinical examination that included, among other items, standardized measurements of height, weight and waist circumference.[11] The HUNT

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study database is regularly updated with information on site of residence and vital status from the Norwegian population registry.

Body mass index (BMI) was calculated as weight in kilograms over squared height in metres and categorized according to World Health Organization (WHO) recommendations as < 18.5 (underweight), 18.5–24.9 (normal weight), 25.0–29.9 (pre-obese), 30.0–34.9 (obese class I), 35.0–39.9 (obese class II) and ≥ 40.0 kg/m^2 (obese class III).[13] As an alternative measure of obesity, we used waist circumference categorized according to WHO as < 94, 94–102 and > 102 cm in males and < 80, 80–88 and > 88 cm in females.[14] Smoking habits were categorized as current, previous or never smoking according to self-report at HUNT2. Participants were asked about their leisure time weekly amount of light (not sweaty or breathless) and vigorous (sweaty or breathless) physical activity during the past year. We categorized participants as being non (no vigorous or light activity), slightly (< 3 h of weekly light activity and no vigorous activity), moderately (≥ 3 h of weekly light activity or < 1 h of vigorous activity) or highly (≥ 1 h of vigorous activity per week) physically active. We used self-reported sitting time as an additional measure of physical inactivity (≤ 4 h, 5–7 h and ≥ 8 h/day). Alcohol consumption was categorized as < 1, 1–7, 8–14 and ≥ 15 glasses/2 weeks; 10.7% of participants only provided information on the frequency of alcohol intake per month. Reported intake of 0 times/month was grouped with < 1 glasses/2 weeks, 1–3 times/month with 1–7 glasses/2 weeks, 4–7 times/month with 8–14 glasses/2 weeks and > 7 times/month with ≥15 glasses/2 weeks. The correlation between these categories of frequency and amount was good, with a Spearman's correlation coefficient of 0.80. For all exposure variables, the reference was the category most closely corresponding to health recommendations, i.e. normal weight, never smokers and at least one weekly hour of vigorous activity (activity generating sweat or breathlessness). For alcohol consumption, 1–7 glasses/2 weeks was set as the reference, because the group of subjects with no alcohol consumption could include subjects that are abstainers for health reasons that may themselves increase the risk of BSI, such as chronic disease and previous alcohol abuse.

Nord-Trøndelag is served by two community hospitals, Levanger Hospital and Namsos Hospital (Nord-Trøndelag Hospital Trust), and St Olavs Hospital in Trondheim serves as the tertiary referral centre. Using the 11-digit unique personal identification number of Norwegian citizens, we linked the HUNT study information to prospectively recorded information on dates and microbes detected in blood cultures at the microbiology laboratories of Levanger and St Olavs Hospitals from 1 January 1995, and from Namsos Hospital from 1 September 1999. Isolates solely consisting of microorganisms commonly associated with skin contamination, such as coagulase-negative *Staphylococcus* species, *Corynebacterium* species and *Propionibacterium* species, were not considered as BSI.[15] BSI mortality was defined as death within 30 days of detection of a BSI, and dates of death were obtained from the Norwegian population register. In participants with multiple positive blood culture specimens, a new episode of BSI was defined as positive blood culture more than 30 days after the previous one.

Statistical analysis

For each outcome (first-time BSI and BSI mortality), we used Cox regression analysis to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) by categories of obesity and lifestyle variables. The participants were followed from the date of participation in HUNT2 between August 1995 and June 1997 for residents having Levanger Hospital as their primary hospital, or from 1 September 1999 for residents having Namsos Hospital as their primary hospital. In the analyses of first-time BSI, participants were followed until their first BSI, migration out of Nord-Trøndelag, death or end of follow-up at 31 December 2011, whichever occurred first. In the analyses of BSI mortality, participants were followed until migration out of Nord-Trøndelag, death or 31 December 2011, whichever occurred first. Before the start of follow-up, 47 (0.07%) participants experienced a positive blood culture, 1140 (1.78%) were censored due to migration or death and 22 were excluded because they lacked information on all exposure variables, leaving 64 027 individuals for the statistical analyses. Primary analyses were adjusted for age (by using age as the underlying time scale) and sex (by stratification). In cohort studies, using age as the underlying time scale has been shown to give a more effective control of age compared with using time on study as time scale while adjusting for age.[16] In a second model, we additionally adjusted for education as a marker of socioeconomic status[17] and for lifestyle factors that could confound the association between the independent variable and BSI.[18,19] The associations of physical activity and sitting time with BSI risk were additionally adjusted for self-reported chronic mobility impairment, defined as chronic physical illness or injury that impaired daily functioning. Other comorbid conditions, such as cardiovascular diseases, were considered possible mediators of the associations between lifestyle and BSI and were not adjusted for. Additionally, we examined associations separately by age at HUNT2 (< or ≥ 65 years) and by sex, as well as the combined effect of obesity, smoking and physical inactivity. We examined

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the combined association of each pair of exposures, to explore whether the association of one exposure may differ by levels of other exposures. To assess how changes in smoking habits and weight were associated with BSI, we examined BSI risk among previous smokers categorized by self-reported time since smoking cessation, and we examined the association of weight change from HUNT1 to HUNT2 with BSI risk overall and by categories of BMI at HUNT1. Finally, we examined the associations of obesity and lifestyle factors with the risk of a first-time BSI with each of the most common infecting microorganisms: *Escherichia coli*, *Streptococcus pneumoniae* and *Staphylococcus aureus*. All analyses were performed using Stata version 13.1 (StataCorp).

Ethics

This study was approved by the Regional Committee for Medical and Health Research Ethics of Central Norway, and all participants signed an informed consent.[11]

Results

During a median follow-up of 14.8 years, amounting to a total of 810 453 person-years of observation for first-time BSI and 816 831 person-years for BSI mortality, 1844 (2.9%) of 64 027 participants experienced at least one episode of BSI, and 396 (0.62%) died from BSI. This corresponds to an incidence rate of 228/100 000 person-years and a mortality rate of 48/100 000 person-years. Baseline characteristics are given in Table 1, and information on infecting microorganisms in Supplementary Table 1, available as Supplementary data at *IJE* online. Information on BMI was available for 63 385 (99.0%) participants, on smoking for 63 541 (99.2%), on alcohol intake for 61 637 (96.3%) and on physical activity for 57 250 (89.4%) participants.

Obesity was associated in a dose-dependent manner with increased risk of BSI and BSI mortality. Compared with normal weight participants (BMI 18.5–24.9 kg/m^2), the age- and sex-adjusted risk of a first-time BSI was 31% (95% CI 14–51%) higher at BMI 30.0–34.9 kg/m^2, 87% (95% CI 50–135%) higher at BMI 35.0–39.9 kg/m^2 and 210% (95% CI 117–341%) higher at BMI $\geq$ 40.0 kg/m^2 (Table 2). The corresponding increase in risk of BSI mortality was 35% (95% CI -1 to 83%) at BMI 30.0–34.9, 144% (95% CI 55–286%) at BMI 35.0–39.9 kg/m^2 and 299% (95% CI 93–724%) at BMI $\geq$ 40.0 kg/m^2, compared with normal weight participants (Table 3).

Associations were essentially unchanged after additional adjustment for lifestyle factors and level of education. Using waist circumference as an alternative measure of obesity, we observed associations between wider waist circumference and higher risks of BSI and BSI mortality similar to those observed for BMI (Supplementary Table 2, available as Supplementary data at *IJE* online). Low BMI ($<$ 18.5 kg/m^2) was associated with increased risk of BSI in age- and sex-adjusted analysis (75% increased risk, 95% CI 5–193%), but the statistical evidence for this association was weakened in multivariable adjusted analysis (41% increased risk, 95% CI -30 to 185%) (Table 2). For 71% of participants, weight and BMI were also available from the HUNT1 Survey 11 years preceding HUNT2.

Table 1. Baseline characteristics[a] of 64 027 participants in the HUNT Study, Norway 1995–97

Variable	Total population (n = 64027)	BSI during follow-up (n = 1844)
Age, median (IQR)	48.6 (36.4–63.6)	67.7 (55.5–74.7)
Female sex, *n* (%)	34079 (53.2)	898 (48.7)
Highest education achieved, *n* (%)		
$\leq$ 9 years	22170 (36.5)	952 (57.7)
10–12 years	26452 (43.6)	532 (32.2)
$>$ 12 years	12062 (19.9)	167 (10.1)
Chronic mobility impairment, *n* (%)		
None	55084 (86.0)	1414 (76.7)
Slight	3661 (5.7)	134 (7.3)
Moderate	2848 (4.5)	145 (7.9)
Severe	2434 (3.8)	151 (8.2)
BMI kg/m^2, mean (SD)	26.4 (4.1)	27.7 (4.6)
Waist circumference cm, mean (SD)	86.4 (11.7)	91.7 (12.5)
Smoking, *n* (%)		
Never	28880 (45.5)	703 (38.6)
Previous	16505 (26.0)	626 (34.3)
Current	18156 (28.6)	494 (27.1)
Alcohol intake, *n* (%)		
$<$ 1 glass/2 weeks	22787 (37.0)	906 (52.4)
1–7 glasses/2 weeks	30395 (49.3)	665 (38.5)
8–14 glasses/2 weeks	6531 (10.6)	115 (6.7)
$\geq$ 15 glasses/2 weeks	1924 (3.1)	42 (2.4)
Physical activity,[b] *n* (%)		
None	4642 (8.1)	207 (14.7)
Slight	17816 (31.1)	497 (35.4)
Moderate	19344 (33.8)	447 (31.8)
High	15448 (27.0)	253 (18.0)
Sitting time, *n* (%)		
$\leq$ 4 h/day	15416 (31.5)	447 (33.5)
5–7 h/day	15668 (32.0)	444 (33.3)
$\geq$ 8 h/day	17927 (36.6)	443 (33.2)

[a]% refers to the proportion within the total population or those with BSI, respectively.

[b]None, no light or vigorous activity; slight, $<$ 3 h light activity/week and no vigorous activity; moderate, $\geq$ 3 h light activity or $<$ 1 h vigorous activity/week; high, $\geq$ 1 h vigorous activity/week.

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Table 2. Associations of BMI and lifestyle factors with the risk of bloodstream infection among 64 027 participants in the HUNT Study, Norway 1995–2011

Lifestyle variable	Age- and sex-adjusted					Age-, sex-, education- and lifestyle-adjusted[a]				
	Person-years at risk	No. BSI	Incidence rate per 100 000 person-years	HR	95% CI	Person-years at risk	No. BSI	Incidence rate per 100 000 person-years	HR	95% CI
BMI, kg/m^2										
< 18.5	5270	15	285	1.75	1.05–2.93	4402	8	182	1.41	0.70–2.85
18.5–24.9	321042	523	163	1.00	Reference	288423	388	135	1.00	Reference
25.0–29.9	348025	817	235	1.04	0.93–1.17	302915	568	188	1.02	0.90–1.17
30.0–34.9	103982	339	326	1.31	1.14–1.51	85412	234	274	1.38	1.17–1.63
35.0–39.9	21404	90	420	1.87	1.50–2.35	17137	58	338	1.77	1.34–2.35
≥ 40.0	5196	33	635	3.10	2.17–4.41	4181	23	550	3.14	2.05–4.81
Smoking										
Never	367417	703	191	1.00	Reference	317988	451	142	1.00	Reference
Previous	206261	626	304	1.30	1.16–1.46	180356	464	257	1.31	1.14–1.51
Current	231577	494	213	1.51	1.34–1.70	203405	364	179	1.53	1.32–1.78
Physical activity level[b]										
None	53199	207	389	1.71	1.42–2.07	48098	170	353	1.41	1.15–1.74
Slight	228970	497	217	1.18	1.01–1.38	216129	455	210	1.10	0.93–1.30
Moderate	250954	447	178	1.00	0.85–1.17	239738	417	174	0.97	0.83–1.15
High	204086	253	124	1.00	Reference	197784	237	120	1.00	Reference
Alcohol intake										
< 1 glass/2 weeks	272422	906	333	1.01	0.91–1.13	219150	572	261	0.97	0.85–1.10
1–7 glasses/2 weeks	401370	665	166	1.00	Reference	377542	569	151	1.00	Reference
8–14 glasses/2 weeks	85625	115	134	0.89	0.73–1.09	81741	100	122	0.86	0.69–1.06
≥ 15 glasses/2 weeks	24312	42	173	1.24	0.91–1.70	23316	38	163	1.21	0.87–1.69

[a]Adjusted for age, sex, education, smoking, BMI, physical activity and alcohol intake. The association of physical activity with BSI risk was additionally adjusted for chronic mobility impairment.

[b]None, no light or vigorous activity; slight, < 3 h light activity/week and no vigorous activity; moderate, ≥ 3 h light activity or < 1 h vigorous activity/week; high, ≥ 1 h vigorous activity/week.

Most participants remained in their BMI category between the surveys (Supplementary Table 3, available as Supplementary data at *IJE* online), but there was a mean weight gain of 4.6 kg [standard deviation (SD) 6.7 kg]. Weight loss was associated with an increased risk of subsequent BSI, whereas weight gain was not meaningfully associated with increased BSI risk except when weight increased by 10 kg or more. The association of weight change with BSI risk was similar across BMI categories (Supplementary Table 4, available as Supplementary data at *IJE* online).

Compared with never smokers, the age- and sex-adjusted risk of a first time BSI was 51% (95% CI 34–70%) higher among current smokers and 30% (95% CI 16–46%) higher among previous smokers (Table 2). For BSI mortality, there was a 75% (95% CI 34–129%) increase in risk among current smokers and 30% (95% CI 1–68%) increase in risk among former smokers. After additional adjustment for education, obesity and lifestyle factors, the effect estimates were unchanged for BSI risk and slightly increased for BSI mortality (Table 3). Among previous smokers, the risk of BSI was highest among those who had recently quit smoking (Supplementary Table 5, available as Supplementary data at *IJE* online).

Physically inactive participants had a 71% (95% CI 42–107%) increased risk of first-time BSI and 108% (95% CI 37–216%) increased risk BSI mortality compared with those undertaking at least 1 h of vigorous exercise per week. In multivariable adjusted analyses, the risk was attenuated to 41% (95% CI 15–74%) and 70% (95% CI 6–174%) higher risks of BSI and BSI mortality, respectively. We found no increased risk of BSI or BSI mortality associated with sitting time (Supplementary Table 2) or alcohol consumption (Table 3). The observed associations did not differ convincingly by age (Supplementary Table 6, available as Supplementary data at *IJE* online) or sex (Supplementary Table 7, available as Supplementary data at *IJE* online).

The association of each exposure with BSI risk was broadly similar across levels of other exposures (Supplementary Table 8, available as Supplementary data

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Table 3. Associations of BMI and lifestyle factors with mortality from bloodstream infection[a] among 64 027 participants in the HUNT Study, Norway 1995–2011

Lifestyle variable	Age-and sex-adjusted					Age-, sex-, education-, and lifestyle-adjusted[b]				
	Person-years at risk	No. BSI deaths	Mortality rate per 100 000 person-years	HR	95% CI	Person-years at risk	No. BSI deaths	Mortality rate per 100 000 person-years	HR	95% CI
BMI, kg/m^2										
< 18.5	5323	2	38	1.20	0.30–4.88	4445	1	23	0.96	0.13–6.94
18.5–24.9	323165	101	31	1.00	Reference	290075	71	24	1.00	Reference
25.0–29.9	350823	183	52	1.12	0.88–1.43	304978	117	38	1.09	0.81–1.47
30.0–34.9	105218	72	68	1.35	0.99–1.83	86296	48	56	1.49	1.02–2.17
35.0–39.9	21806	23	105	2.44	1.55–3.86	17420	15	86	2.56	1.45–4.53
≥ 40.0	5316	8	150	3.99	1.93–8.24	4272	7	164	5.67	2.56–12.58
Smoking										
Never	370124	150	41	1.00	Reference	320130	82	26	1.00	Reference
Previous	208458	137	66	1.30	1.01–1.68	182284	98	54	1.47	1.06–2.04
Current	233420	106	45	1.75	1.34–2.29	205073	79	39	2.23	1.59–3.14
Physical activity level[c]										
None	53918	51	95	2.08	1.37–3.16	48751	40	82	1.70	1.06–2.74
Slight	230884	107	46	1.39	0.97–2.00	218140	98	45	1.42	0.96–2.11
Moderate	252722	94	37	1.14	0.79–1.64	241663	85	35	1.19	0.80–1.77
High	205083	43	21	1.00	Reference	198931	36	18	1.00	Reference
Alcohol intake										
< 1 glass/2 weeks	275556	206	75	0.96	0.76–1.22	221482	122	55	0.89	0.67–1.19
1–7 glasses/2 weeks	404120	130	32	1.00	Reference	380317	108	28	1.00	Reference
8–14 glasses/2 weeks	86088	26	30	1.05	0.69–1.60	82233	22	27	0.98	0.62–1.56
≥ 15 glasses/2 weeks	24451	9	37	1.35	0.68–2.66	23453	7	30	1.13	0.52–2.45

[a]Defined as death within 30 days after detection of a BSI.

[b]Adjusted for age, sex, education, smoking, BMI, physical activity and alcohol intake. The association of physical activity with risk of BSI mortality was additionally adjusted for chronic mobility impairment.

[c]None, no light or vigorous activity; slight, < 3 h light activity/week and no vigorous activity; moderate, ≥ 3 h light activity or < 1 h vigorous activity/week; high, ≥ 1 h vigorous activity/week.

at *IJE* online), except that the association of alcohol consumption differed by levels of BMI (Pinteraction = 0.006). Normal weight participants with high alcohol consumption had increased risk of BSI compared with normal weight participants with low alcohol consumption [hazard ratio (HR) 2.26, 95% CI 1.40–3.65), but a similar association was not seen at higher BMI levels.

To assess the combined effect of obesity, smoking and low physical activity, we examined BSI risk among obese (BMI ≥ 35.0 kg/m^2) current smokers undertaking no or slight physical activity. In these individuals, the age- and sex-adjusted risk of BSI was nearly 5-fold increased (HR 4.78, 95% CI 2.44–9.35), and the risk of BSI mortality more than 6-fold increased (HR 6.42, 95% CI 1.83–22.59), compared with normal weight never smokers with a moderate or high activity level. In crude rates, this corresponded to 414 BSIs and 121 deaths from BSI per 100 000 person-years in the high-risk group, and 61 BSIs and 13 deaths from BSI per 100 000 person-years in the comparison group.

In analyses of BSI by the most common bacteria (Table 4), obesity was associated in a dose-dependent manner with a strongly increased risk of BSI with *Staphylococcus aureus* (HR 8.24, 95% CI 3.88–17.51 at BMI ≥ 40 kg/m^2) and also with increased risk of BSI with *Escherichia coli* (HR 2.65, 95% CI 1.48–4.77 at BMI ≥ 40 kg/m^2) compared with the normal weight participants. In contrast, there was no association between increased BMI and risk of BSI with *Streptococcus pneumoniae*. Smoking was strongly associated with increased risk of *Streptococcus pneumoniae* BSI with a 207% (95% CI 119–330%) and 63% (95% CI 13–135%) risk increase among current and previous smokers respectively, compared with never smokers. There were similar, but weaker, associations between smoking and increased risk of BSI with *Staphylococcus aureus* or *Escherichia coli*. Physical inactivity was associated with a 149% (95% CI 42–335%) increased risk of BSI with *Staphylococcus aureus* and a 53% (95% CI 9–114%) increased risk of E*scherichia coli*

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Table 4. Age- and sex-adjusted hazard ratios of bloodstream infection by the three most common microorganisms among 64 027 participants in the HUNT Study, Norway 1995–2011

	Escherichia coli			*Staphylococcus aureus*			*Streptococcus pneumoniae*		
Lifestyle variable	No. BSI / person-years at risk	HR	95% CI	No. BSI / person-years at risk	HR	95% CI	No. BSI / person-years at risk	HR	95% CI
BMI, kg/m^2									
< 18.5	6/5270	1.78	0.79–4.02	1/5270	1.16	0.16–8.40	4/5270	2.97	1.08–8.12
18.5–24.9	192/321042	1.00	Reference	56/321042	1.00	Reference	82/321042	1.00	Reference
25.0–29.9	296/348025	1.04	0.87–1.25	86/348025	0.99	0.70–1.39	110/348025	0.94	0.70–1.25
30.0–34.9	132/103982	1.32	1.06–1.66	47/103982	1.75	1.18–2.59	28/103982	0.73	0.47–1.13
35.0–39.9	38/21404	1.95	1.37–2.77	10/21404	2.15	1.09–4.25	6/21404	0.83	0.36–1.91
≥ 40.0	12/5196	2.65	1.48–4.77	8/5196	8.24	3.88–17.51	1/5196	0.61	0.09–4.42
Smoking									
Never	288/367417	1.00	Reference	76/367417	1.00	Reference	63/367417	1.00	Reference
Previous	230/206261	1.36	1.12–1.64	73/206261	1.24	0.88–1.76	70/206261	1.63	1.13–2.35
Current	160/231578	1.35	1.10–1.66	60/231578	1.59	1.12–2.27	96/231578	3.07	2.19–4.30
Physical activity level[a]									
None	69/53199	1.53	1.09–2.14	27/53199	2.49	1.42–4.35	19/53199	1.24	0.70–2.20
Slight	172/228970	1.13	0.86–1.48	62/228970	1.64	1.02–2.64	63/228970	1.10	0.72–1.68
Moderate	170/250954	1.10	0.84–1.44	49/250954	1.17	0.72–1.91	68/250954	1.12	0.74–1.69
High	79/204086	1.00	Reference	25/204086	1.00	Reference	36/204086	1.00	Reference

[a]None, no light or vigorous activity; slight, < 3 h light activity/week and no vigorous activity; moderate, ≥ 3 h light activity or < 1 h vigorous activity/week; high, ≥ 1 h vigorous activity/week.

compared with the most active group. There was no association between physical inactivity and BSI with *Streptococcus pneumoniae*.

Discussion

In this large population-based cohort study, obesity, smoking and physical inactivity were associated with increased risks of BSI and BSI mortality. These results underscore that lifestyle factors may be important for the risk of acquiring invasive infections, a risk which could be attenuated by lifestyle interventions.

The strengths of this study include the population-based design and linkage to prospectively recorded information on BSI from microbiology laboratories at the local and regional hospitals. Due to the large sample size we could assess the risk of any BSI, BSI mortality and the risk of BSI by infecting organism, which expands our understanding of the influence obesity and lifestyle factors exert on the burden of BSI. We did not have clinical information about the course of infection after registration of a positive blood culture; however, review of medical records of patients with *Staphylococcus aureus* and *Streptococcus pneumoniae* BSI in this study population has shown that 98.4% and 98.6% of patients met the 2001 sepsis criteria, respectively.[20,21] Further, we excluded pathogens most commonly associated with contamination, and the majority of positive culture episodes in this material are likely to represent serious infections. Obesity measures were obtained by standardized clinical examination, whereas the other exposure information was self-reported. The self-reported information on vigorous exercise in HUNT has been shown to correlate moderately well with oxygen uptake in healthy adults, whereas the association was less clear for self-report of light exercise.[22]

The exposures were measured up to 15 years before the outcome. We would likely have obtained similar results if exposures had been measured closer to the outcome, because our exposure variables represent quite stable traits in most participants. However, the long time span from exposure measurement to outcome may be an advantage if diseases predisposing to BSI may have influenced our exposure variables. Despite the strong association between obesity and increased BSI risk that we observed, weight loss was more strongly than weight gain associated with increased risk of subsequent BSI. Weight loss among middle-aged or elderly individuals is often unintentional and caused by ill health,[23] and the association of weight loss with increased BSI risk may represent confounding by ill health.

Although few studies have assessed a comprehensive set of lifestyle factors with a wide range of infections, associations between single lifestyle factors and specific types of infection have been reported previously. Obesity has been identified as a risk factor for nosocomial infections,[24] but the population-level impact of obesity on the risk of severe

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infections has received less attention.[5,25] Obesity was associated with increased sepsis risk in one cohort study of 30 000 subjects, with a 50% increased risk at BMI 30–39.9 kg/m^2 and 2-fold increased risk at BMI $\geq$ 40 kg/m^2.[8] Abdominal obesity, indicated by increased waist circumference, has been associated with an a 1.7-fold increased risk of sepsis mortality.[10] Our results add to that evidence by demonstrating clear dose-response relationships of obesity with BSI and BSI mortality as well as showing that the importance of obesity as a risk factor varied by infecting organism. Possibly, variation in infecting organisms between studies may explain why previous reports of the association between obesity and of pneumonia have reported conflicting results.[7,26]

Smoking is well established as a risk factor for airways infection as well as sepsis,[6,27,28] whereas the association between smoking and non-airways bacterial infections has received less attention. The 3-fold increased risk of BSI with *Streptococcus pneumoniae* in our study is likely explained by an increased risk of airways infections in smokers. Nonetheless, smoking was also associated with BSI with *Staphylococcus aureus* and *Escherichia coli,* which are less often causes of airway infections. Our finding that smoking is associated with an increased risk of BSI mortality as well as BSI risk is in line with a recent study, where infections were added to conditions that contribute to excess mortality from smoking.[29]

Low amounts of exercise were associated with $\sim$ 50% increased risk of sepsis in a population-based cohort[9] and with $\sim$ 50% increased risk of sepsis mortality in a study population of walkers and runners;[10] our study extends these findings to a general adult population.

Previous studies have identified an association between excessive alcohol intake and the risk of severe infections such as pneumonia and sepsis.[4,7] The role of a moderate alcohol intake has been less clear.[26,30] We did not detect any association between alcohol intake and risk of BSI in the main analysis, but high alcohol intake was associated with an increased risk of BSI among normal weight participants. We have no explanation why an adverse effect of alcohol on BSI risk should be stronger at normal weight, and this sub-group finding should be interpreted with caution. Few HUNT participants reported a very high alcohol intake, and we had limited possibility to study BSI risk related to excess alcohol intake.

The associations identified in this study could be due to effects of lifestyle factors on the immune system or of mechanical factors related to infection susceptibility, or could be mediated through an increased risk of non-communicable diseases. Obesity, smoking and inactivity are associated with increased risk of diseases such as diabetes, cardiovascular disease, cancer and renal disease,[31,32] which all are associated with an increased risk of bacterial infections[4,30] or mortality from bacterial infections.[33] Obesity has been identified as a risk factor for *Staphylococcus aureus* nasal carriage,[34] which is associated with a 3-fold increased risk of nosocomial *Staphylococcus aureus* BSI.[35] Other plausible mechanisms include alterations in immune function. Obesity is associated with alterations in the interaction between metabolic and immune processes,[36] smoking exerts an inhibitory effect on the immune system through several pathways[37] and exercise may have immunomodulatory effects.[38]

The worldwide obesity prevalence has increased substantially over past decades[39] and, despite reductions in cigarette consumption in some countries, the overall global consumption is still on the rise.[40] Coupled with this, infectious diseases are among the most common causes of disease burden globally, particularly in developing countries. With combined effects of obesity, smoking and inactivity increasing the risk of BSI and BSI mortality 5- to 6-fold at the population level, it is likely that facilitating healthy lifestyle choices and halting the obesity epidemic may have a substantial impact on reducing the global risk of invasive bacterial infections.

Supplementary Data

Supplementary data are available at *IJE* online.

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