Obesity and Risk of Infection

Results from the Danish Blood Donor Study

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Background: It is well known that obesity complicates the course of several diseases. However, it is unknown whether obesity affects the risk of infection among healthy individuals.

Methods: We included 37,808 healthy participants from the Danish Blood Donor Study, who completed a questionnaire on health-related items. Obesity was defined as a body mass index ≥ 30 kg/m^2. Infections among participants were identified by relevant ICD-10 codes in the Danish National Patient Register and Anatomical Therapeutic Chemical (ATC) codes in the Danish Prescription Register. Multivariable Cox proportional hazards analysis with age as the underlying timescale was used as the statistical model.

Results: During 113,717 person-years of observation, 1,233 participants were treated for infection at a hospital. Similarly, during 58,411 person-years of observation, 15,856 participants filled at least one prescription of antimicrobials. Obesity was associated with risk of hospital-based treatment for infection (women: hazard ratio [HR] = 1.5, 95% confidence interval [CI] = 1.1, 1.9; men: HR = 1.5, 95% CI = 1.2, 1.9). For specific infections, obesity was associated with increased risk of abscesses (both sexes), infections of the skin and subcutaneous tissue (men), and respiratory tract infections and cystitis (women). Similarly, obesity was associated with filled prescriptions of antimicrobials overall (women: HR = 1.22, 95% CI = 1.14, 1.30; men: HR = 1.23, 95% CI: 1.15, 1.33) and particularly with phenoxymethylpenicillin, macrolides, dicloxacillin and flucloxacillin, and broad-spectrum penicillins.

Conclusions: In a large cohort of healthy individuals, obesity was associated with risk of infection. This result warrants further studies of metabolism and the immune response.

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According to the World Health Organization (WHO), more than 500 million adults are obese. Globally, obesity kills more people than does underweight.[1]

Obesity is associated with an increased risk of a range of diseases, such as metabolic syndrome, cardiovascular diseases, and diabetes.[2] Risk of infection is increased among obese patients with various comorbidities and obese individuals are more likely to acquire infections at surgical sites.[3] Furthermore, obesity is associated with *Streptococcus pyogenes* infection.[4] One study showed an increased risk of community-acquired respiratory tract infections in nonhospitalized women.[5] Most studies of the association between obesity and infection risk, however, have been carried out in the setting of other comorbidities.

Obesity has consequences that may increase risk of infection at certain anatomical sites. For example, skin folds may increase the risk of skin infections. Obesity also has immunologic consequences that have recently attracted scientific interest. Adipose tissue is involved in the regulation of energy metabolism and contributes to systemic low-grade inflammation with slightly elevated C-reactive protein.[6–9] Obesity is the most common cause of insulin resistance and, consequently, type 2 diabetes,[10] and patients with type 2 diabetes are at increased risk of infection.[11]

Blood donors are a highly selected, healthy population, simply because they fulfill certain criteria regarding health status and lifestyle to be accepted as donors. We therefore examined whether obesity was related to a higher risk of infection in a large cohort of healthy individuals.

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MATERIALS AND METHODS

Participants

We included participants from the Danish Blood Donor Study, which was initiated in 2010 as a multicenter public-health study and biobank (www.dbds.dk). Currently, more than 90,000 donors from the Capital Region of Denmark, Region Zealand, the Central Denmark Region and the North Denmark Region participate. Repeat donors, age 18–67 years, were asked to enter the study after oral and written information had been given. If the donor agreed to participate, he or she filled out a four-page questionnaire, and blood samples were stored. The questionnaire addressed smoking status, alcohol consumption, physical activity, diet, anthropometric measurements, and (among women) use of contraception, childbirth, and menopausal status. Participants also gave permission to collect data on health and demographics from public registries. Fewer than 5% of donors declined to participate.

From March 2010 to December 2012, a total of 41,678 participants were included in DBDS. We excluded participants if they had missing responses to the following questionnaire items: current smoking status (2,925 participants), height (2,917), and weight (2,655). For waist circumference, 5,382 responses were missing and these participants were excluded only from analyses in which waist circumference was used as a predictor. In total, 1,827 women and 2,043 men were excluded from the analysis with body mass index (BMI) as predictor, and 3,220 women and 3,397 men were excluded from the analysis with waist circumference as predictor.

Identification and Classification of Infection

Follow-up data was collected from the Danish National Patient Register and the Danish National Prescription Register from the date the blood donor was included in the study.

The Danish National Patient Register (NPR) was established in 1977 and covers somatic as well as psychiatric in- and outpatients of all Danish hospitals.[12,13] The NPR maintains a record of all hospital visits with information on dates of admission and discharge. Diagnostic information was based on the International Classification of Diseases, Tenth Revision (ICD-10) valid from 1994 to the present.[14]

We included both admissions and outpatient contacts. The following types of diagnostic codes were used: A (primary diagnosis), B (secondary diagnosis), and G (underlying medical condition). ICD-10 codes covering infection were used to classify endpoints. Chronic infections (other than chronic tonsillitis), condyloma, fungal infections, and parasitic infections were all excluded.

Where possible, we grouped infections as abscesses, infections of the skin and subcutaneous tissue, respiratory tract infections, ear infections, gastrointestinal infections, urinary tract infections, or pelvic inflammatory diseases. These groups were further divided into relevant subgroups. See the eAppendix (http://links.lww.com/EDE/A910) for specific ICD-10 codes, as well as the exceptions in each of the diagnostic code subgroups.

We used Charlson's Comorbidity Index to address comorbidity as a potential confounding factor.[15] This score includes 17 major disease categories identified by ICD-10 codes, and includes congestive heart failure, chronic pulmonary disease, cerebrovascular disease, dementia, rheumatic disease, diabetes, renal disease, cancer, liver disease, and AIDS.[15] Each comorbidity was given a weighted score. Hypertension (ICD-10: I10, I11, I13, and I15), gastro-esophageal reflux (ICD-10: K21),[16] and atrial fibrillation (ICD-10: I48)[17] were added to the index, each weighted one point. The Charlson Index for each participant was determined as a cumulative score for 15 years before inclusion, and grouped as Charlson Index 0 (no comorbidity), Charlson Index 1 (participants with a score of 1), and Charlson Index 2 (participants with a score above one).

The Danish National Prescription Register was established in 1994 and retains key information on all prescribed drugs dispensed from all pharmacies in Denmark. This information includes the unique personal identification number of the patient, the type of drug according to Anatomical Therapeutic Chemical (ATC) classification system, and the date of prescription.[18]

We identified filled prescriptions for all antimicrobial agents prescribed for oral treatment of bacterial (J01x) or viral infections (J05x) and established specific groups of antimicrobials to reflect the treatment of infections with various anatomical locations. National Danish guidelines for primary care was used for this purpose and the groups have been listed below.[19,20] Respiratory tract infections are most often treated with phenoxymethylpenicillin (J01CE02) and macrolides (erythromycin: J01FA01, roxithromycin: J01FA06, and clarithromycin: J01FA09). Phenoxymethylpenicillin is the first choice treatment against community-acquired respiratory tract infections. Macrolides are mainly prescribed when a patient is allergic to penicillin or for treatment of mycoplasma pneumonia. Dicloxacillin (J01CF01) and flucloxacillin (J01CF05) are used for the treatment of skin infections. For fungal skin infections, topical treatment with antifungals (miconazole: D01ACO2, D01AC52 and terbinafine: D01AE15, D01BA02) can be chosen. Azithromycin (J01FA10) is used against chlamydial infection. Pivmecillinam (J01CA08) and sulfamethizole (J01EB02) are the main antimicrobials for treatment of acute uncomplicated urinary tract infections. In an additional analysis, further antimicrobials for treatment of urinary tract infections were included (pivmecillinam, sulfamethizole, nitrofurantoin: J01XE01, trimethoprim: J01EA01, and ciprofloxacin: J01MA02). We also analyzed broad-spectrum penicillins, even though no definite anatomic localization of the infection can be deduced from the prescription of these antimicrobials: pivampicillin (J01CA02), amoxicillin (J01CA04), and amoxicillin with enzyme inhibitor (J01CR02). Ampicillin and amoxicillin are active against certain strains of

Escherichia coli, *Proteus mirabilis*, *Salmonella, Shigella*, and *Haemophilus influenzae*. The combination of amoxicillin with clavulanate is active against many bacterial organisms that cause, e.g., sinusitis, otitis media, skin and tissue infections, exacerbation of chronic bronchitis, pneumonia, and urinary tract infections.[21]

Classification of Obesity

We categorized each participant according to BMI using WHO definitions: BMI < 18.5 (underweight), 18.5 ≤ BMI < 25 (normal weight: reference), 25 ≤ BMI < 30 (overweight), and BMI ≥ 30 (obese).[22] Persons weighing less than 50 kg cannot become blood donors in Denmark. Underweight people are thus poorly represented in our study; indeed, less than 0.7% (252) of the participants was defined as underweight. We therefore excluded underweight participants from analyses involving BMI stratification.

According to WHO, the recommendations of waist circumference cut-off points for increased risk of metabolic complications are 80 cm for women and 94 cm for men, but more than 50% of the participants had waist circumferences above these limits. Instead, we categorized participants with a waist circumference in the upper 10th percentile for their sex as having central obesity. The corresponding values of waist circumference were 99 cm for women and 106 cm for men.

Statistical Analysis

We used Multivariable Cox proportional hazards analysis to determine the relative risk of infection according to obesity (yes/no) or abdominal obesity (yes/no) as defined above. Age was used as the underlying timescale, and adjustments for current smoking status at baseline (yes/no), and comorbidity (using Charlson's Comorbidity Index, categorized as mentioned above) were included in an adjusted model. Study participants were followed for infections (defined as above) from date of inclusion in DBDS until either emigration, death or end of follow-up, which was December 31, 2013, for analyses, with diagnosis codes as the outcome or December 31, 2012, for analyses with filled prescriptions as the outcome.

Trend tests regarding the effect of obesity were based on the calculated BMI as a continuous variable.

Interactions between obesity and current smoking status and between obesity and Charlson Index were included in all models to facilitate an unambiguous interpretation of the main effect of obesity, current smoking, and Charlson Index. Furthermore, all proportionality assumptions, used in the models, were visually checked before use by plotting the observed and the fitted survival curves and log–log plots.

We decided a priori to stratify the analyses by sex.[5,16]

Data are presented as numbers, medians with ranges, or frequency statistics. Risk estimates are presented as hazard ratios (HR) with 95% confidence intervals (CI).

Incidence rates are shown as events per year at risk.

Statistical analysis was performed using Stata/MP 13.1 for Windows (StataCorpLP, College Station, TX).

Ethics

Oral and written informed consent was obtained from all participants. The Ethical Committee of Central Denmark (M-20090237) approved the study. In addition, the biobank and research database were approved by the Danish Data Protection Agency (2007-58-0015).

RESULTS

Characteristics of the Cohort

The characteristics of the cohort are presented in Table 1. Within the 113,717 person-years of observation based on 37,808 participants, a total of 1,233 individuals received treatment for infection at a hospital. Hospital-based outpatient visits constituted 346 (28%) of the 1,233 cases. In addition, 15,856 participants filled at least one prescription of antimicrobials during 58,411 person-years of observation. Risk estimates, including waist circumference, were based on 35,061 participants (48% women, 52% men) of whom 1,149 were treated at a hospital for infection during 105,588 person-years of observation, whereas

TABLE 1. Characteristics of the Cohort Stratified by Sex

	Women	Men
Numbers of participants	18,120 (48%)	19,688 (52%)
Age (year)		
≤30	5,653	4,756
31–40	4,227	4,974
41–50	4,298	4,869
51–60	2,898	3,538
>60	1,044	1,551
Age (years)	38.1 (27.6; 48.4)	40.2 (30.3; 50.5)
Weight (kg)	68 (62.0; 76.0)	83 (76.0; 92.0)
Height (cm)	169 (165; 173)	182 (178; 187)
Waist (cm)	82 (76.0; 90.0)	92 (86.0; 99.0)
BMI (kg/m^2)	23.6 (21.7; 26.3)	25.1 (23.3; 27.5)
Current smoker	3,003 (17%)	3,135 (16%)
BMI, categorized (kg/m^2)		
BMI < 18.5 (underweight)	194 (1%)	58 (<1%)
18.5 ≤ BMI < 25 (normal weight)	11,522 (64%)	9,525 (48%)
25 ≤ BMI < 30 (overweight)	4,543 (25%)	8,096 (41%)
BMI ≥ 30 (obese)	1,861 (10%)	2,009 (10%)
Waist circumference, categorized (cm)		
Women, waist < 99; men, waist < 106	15,014 (90%)	16,411 (90%)
Woman, waist ≥ 99; men, waist ≥ 106	1,713 (10%)	1,923 (10%)
Treated for infection at a hospital	575 (3%)	658 (3%)
Filled prescriptions of antimicrobials	9,053 (50%)	6,803 (35%)
Charlson's Comorbidity Index[a]		
0	17,493 (97%)	19,011 (97%)
1	569 (3%)	612 (3%)
2	58 (<1%)	65 (<1%)

Numbers with percentages or medians with interquartile ranges.

[a]Charlson's Comorbidity Index was determined as a cumulated score 15 years before inclusion.

14,677 participants filled at least one prescription of antimicrobials during 54,309 person-years of observation.

Participants with obesity (BMI ≥ 30) constituted 10% of both women and men, respectively; and overweight (25 ≤ BMI < 30) participants constituted 25% and 41% of women and men, respectively.

Obesity and Risk of Infection

The association between obesity and the risk of being treated for infection at a hospital is presented in Table 2, along with relevant infection subgroups.

Obesity was associated with an increased risk of infections overall for women (HR = 1.5, 95% CI = 1.1, 1.9) and men (HR = 1.5, 95% CI = 1.2, 1.9). The strongest associations were observed for abscesses (both sexes), infections of the skin and subcutaneous tissue among men, and respiratory tract infections and cystitis among women. In a separate analysis involving only hospital-based outpatient visits, the HRs for infections overall were 1.3 (95% CI = 0.8, 2.1) for women and 1.6 (95% CI = 1.0, 2.4) for men.

Figure 1 shows the association between BMI strata and the most relevant infection groups. We found a consistent trend toward higher risk in the higher BMI strata. Whereas the association between infection and obesity was the most pronounced, overweight participants were also at higher risk for some infection groups compared with normal-weight participants (Figure 1). In Figure 1, when performing trend tests based on the calculated BMI as a continuous variable, trends were observed for infections overall, abscesses, infections of the skin and subcutaneous tissue among men, and respiratory tract infections among women. Similar results were found for waist circumference (see eAppendix Table 1; http://links.lww.com/EDE/A910).

TABLE 2. The Association Between Obesity and Infection

	Women				Men			
			Crude[c]	Adjusted[d]			Crude	Adjusted
Site of Infection	N[a]	IR[b]	HR (95% CI)	HR (95% CI)	N	IR	HR (95% CI)	HR (95% CI)
Infections overall								
BMI < 30 (reference)	499	10.2	1	1	563	10.6	1	1
BMI ≥ 30	76	13.6	1.5 (1.1, 1.9)	1.5 (1.1, 1.9)	95	15.7	1.5 (1.2, 1.9)	1.5 (1.2, 1.9)
Abscesses								
All abscesses								
BMI < 30 (reference)	84	1.7	1	1	111	2.1	1	1
BMI ≥ 30	21	3.7	2.3 (1.4, 3.8)	2.3 (1.4, 3.7)	28	3.1	2.4 (1.5, 3.6)	2.3 (1.5, 3.6)
Infections of the skin and subcutaneous tissue								
All infections of the skin and subcutaneous tissue								
BMI < 30 (reference)	80	1.6	1	1	162	3.0	1	1
BMI ≥ 30	7	1.2	0.9 (0.4, 1.9)	0.9 (0.4, 1.9)	39	6.3	2.2 (1.6, 3.2)	2.2 (1.6, 3.2)
Erysipelas								
BMI < 30 (reference)	15	0.3	1	1	29	0.5	1	1
BMI ≥ 30	0	-	-	-	9	1.5	2.5 (1.2, 3.3)	2.5 (1.2, 5.3)
Other								
BMI < 30 (reference)	66	1.3	1	1	135	2.5	1	1
BMI ≥ 30	7	1.2	1.1 (0.5, 2.3)	1.1 (0.5, 2.3)	31	5.0	1.1 (0.5, 2.3)	1.1 (0.5, 2.33)
Respiratory tract infections								
All respiratory tract infections								
BMI < 30 (reference)	123	2.5	1	1	125	2.3	1	1
BMI ≥ 30	21	3.7	1.6 (1.0, 2.6)	1.6 (1.0, 2.6)	18	2.9	1.3 (0.8, 2.1)	1.2 (0.8, 2.0)
Tonsillitis								
BMI < 30 (reference)	32	0.6	1	1	23	0.4	1	1
BMI ≥ 30	4	0.7	1.6 (0.6, 4.6)	1.58 (0.6, 4.5)	5	0.8	2.3 (0.9, 6.1)	2.3 (0.9, 6.1)
Pneumonia								
BMI < 30 (reference)	53	1.1	1	1	68	1.3	1	1
BMI ≥ 30	15	2.6	2.4 (1.4, 4.3)	2.4 (1.4, 4.3)	8	1.3	0.9 (0.5, 1.9)	0.9 (0.4, 1.9)
Other								
BMI < 30 (reference)	42	0.8	1	1	40	0.7	1	1
BMI ≥ 30	3	0.5	0.7 (0.2, 2.1)	0.7 (0.2, 2.1)	5	0.8	1.2 (0.5, 3.1)	1.2 (0.5, 3.1)

(Continued)

TABLE 2. (*Continued*)

	Women				Men			
			Crude[c]	Adjusted[d]			Crude	Adjusted
Site of Infection	**N[a]**	**IR[b]**	**HR (95% CI)**	**HR (95% CI)**	**N**	**IR**	**HR (95% CI)**	**HR (95% CI)**
Ear infections								
All ear infections								
BMI < 30 (reference)	20	0.4	1	1	15	0.3	1	1
BMI ≥ 30	1	0.2	0.5 (0.1, 3.7)	0.5 (0.1, 3.7)	5	0.8	2.6 (0.9, 7.3)	2.6 (0.9, 7.2)
Gastrointestinal infections								
All gastrointestinal infections								
BMI < 30 (reference)	109	2.2	1	1	112	2.1	1	1
BMI ≥ 30	15	2.6	1.3 (0.8, 2.2)	1.3 (0.7, 2.2)	12	1.9	0.9 (0.51, 1.7)	0.9 (0.5, 1.6)
Infectious gastrointestinal diseases								
BMI < 30 (reference)	30	0.6	1	1	33	0.6	1	1
BMI ≥ 30	3	0.5	1.1 (0.3, 3.6)	1.0 (0.3, 3.4)	2	0.3	0.5 (0.1, 2.2)	0.5 (0.1, 2.2)
Appendicitis								
BMI < 30 (reference)	55	1.1	1	1	52	1.0	1	1
BMI ≥ 30	6	1.1	1.1 (0.5, 2.7)	1.1 (0.5, 2.7)	5	0.8	0.9 (0.4, 2.2)	0.9 (0.4, 2.2)
Diverticulitis								
BMI < 30 (reference)	26	0.5	1	1	26	0.5	1	1
BMI ≥ 30	5	0.9	1.4 (0.5, 3.6)	1.3 (0.5, 3.5)	4	0.6	1.2 (0.4, 3.3)	1.1 (0.4, 3.3)
Other								
BMI < 30 (reference)	1	0.02	1	1	4	0.07	1	1
BMI ≥ 30	3	0.5	17.4 (1.8, 167.1)	17.9 (1.9, 172.4)	1	0.2	1.7 (0.2, 15.1)	1.6 (0.2, 14.4)
Urinary tract infections								
All urinary tract infections								
BMI < 30 (reference)	66	1.3	1	1	71	1.3	1	1
BMI ≥ 30	14	2.5	2.2 (1.3, 4.8)	2.2 (1.2, 4.0)	4	0.6	0.5 (0.2, 1.4)	0.5 (0.2, 1.4)
Cystitis								
BMI < 30 (reference)	42	0.8	1	1	17	0.3	1	1
BMI ≥ 30	10	1.8	2.4 (1.2, 4.9)	2.4 (1.2, 4.8)	2	0.3	1.1 (0.3, 4.7)	1.1 (0.3, 4.9)
Other								
BMI < 30 (reference)	26	0.5	1	1	56	1.0	1	1
BMI ≥ 30	4	0.7	1.8 (0.6, 5.2)	1.7 (0.6, 4.9)	2	0.3	0.3 (0.1, 1.3)	0.3 (0.1, 1.3)
Pelvic inflammatory diseases								
All pelvic inflammatory diseases								
BMI < 30 (reference)	62	1.3	1	1	-	-	-	-
BMI ≥ 30	8	1.4	1.2 (0.6, 2.6)	1.2 (0.6, 2.5)	-	-	-	-
Pelvic inflammatory diseases (except abscesses)								
BMI < 30 (reference)	48	1.5	1	1	-	-	-	-
BMI ≥ 30	3	0.5	0.6 (0.2, 1.9)	0.6 (0.2, 1.9)	-	-	-	-

Multivariable Cox proportional hazards analysis was performed with BMI ≥ 30 kg/m^2 as predictor.
[a]N: number of cases.
[b]IR: incidence rate per 1000 person-years.
[c]The crude HR was estimated using Cox regression, with age as the underlying time scale.
[d]Multivariable-adjusted model based on the crude model with additional adjustments for current smoking status at baseline and comorbidity using Charlson's Comorbidity Index.

Table 3 and Figure 2 summarize the results for the observed risk associated with obesity and use of antimicrobials. Obesity was associated with the overall use of antimicrobials (women: HR = 1.22, 95% CI = 1.14, 1.30; men: HR = 1.23, 95% CI = 1.15, 1.33). With regard to the specific antimicrobial groups, obesity was most strongly associated with use of phenoxymethylpenicillin, macrolides, dicloxacillin and flucloxacillin, and the broad-spectrum penicillins. However, a reduced risk was observed for pivmecillinam and sulfamethizole prescriptions among obese women. This did not change when we included broad-spectrum antimicrobials used against urinary tract infections. In Figure 2, when performing tests for trend

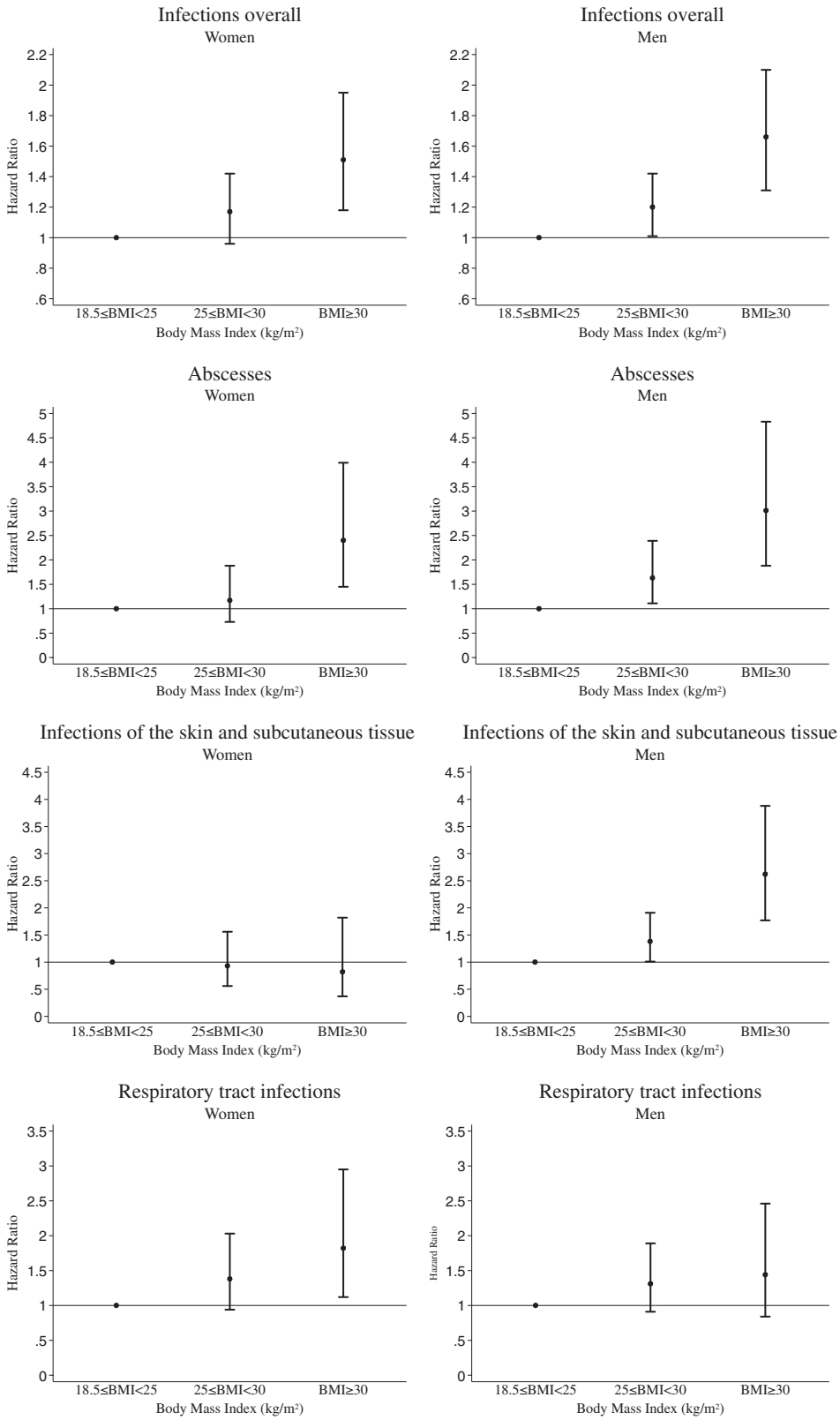

FIGURE 1. The association between BMI strata and infection. Multivariable Cox proportional hazards analysis was performed with BMI strata as predictors, adjusted for smoking status, and comorbidity. Age was used as the underlying timescale. Fewer than 0.7% of the participants were defined as underweight and thus excluded from the analysis. Participants with BMI between 18.5 and 25 were used as reference. *Dots with error bars* Hazard ratios with 95% confidence intervals.

TABLE 3. The Association Between Obesity and Filled Prescriptions of Antimicrobials

			Women				Men	
			Crude[c]	Adjusted[d]			Crude	Adjusted
Type of Prescription	N[a]	IR[b]	HR (95% CI)	HR (95% CI)	N	IR	HR (95% CI)	HR (95% CI)
Antimicrobials overall								
BMI < 30 (reference)	8,051	346.2	1	1	5,999	204.0	1	1
BMI ≥ 30	1,002	396.3	1.23 (1.15, 1.31)	1.22 (1.14, 1.30)	804	250.0	1.24 (1.15, 1.33)	1.23 (1.15, 1.33)
Phenoxymethylpenicillin								
BMI < 30 (reference)	3,847	132.5	1	1	3,511	107.4	1	1
BMI ≥ 30	611	196.6	1.50 (1.38, 1.64)	1.50 (1.37, 1.63)	518	143.8	1.30 (1.19, 1.43)	1.30 (1.18, 1.42)
Erythromycin, roxithromycin, and clarithromycin								
BMI < 30 (reference)	1,187	36.8	1	1	995	27.8	1	1
BMI ≥ 30	199	55.0	1.47 (1.26, 1.71)	1.46 (1.26, 1.70)	146	35.9	1.22 (1.02, 1.45)	1.21 (1.02, 1.45)
Dicloxacillin and flucloxacillin								
BMI < 30 (reference)	704	21.3	1	1	774	21.5	1	1
BMI ≥ 30	113	30.2	1.41 (1.16, 1.73)	1.41 (1.15, 1.72)	137	33.6	1.59 (1.33, 1.91)	1.58 (1.32, 1.90)
Miconazole and terbinafine								
BMI < 30 (reference)	298	8.9	1	1	578	16.0	1	1
BMI ≥ 30	43	11.2	1.25 (0.91, 1.73)	1.25 (0.91, 1.73)	61	14.6	0.92 (0.71, 1.20)	0.92 (0.71, 1.20)
Azithromycin								
BMI < 30 (reference)	905	27.7	1	1	719	19.9	1	1
BMI ≥ 30	95	25.3	1.06 (0.85, 1.31)	1.05 (0.84, 1.29)	72	17.3	0.95 (0.74, 1.21)	0.95 (0.74, 1.21)
Pivmecillinam and sulfamethizole								
BMI < 30 (reference)	2,280	73.5	1	1	228	6.2	1	1
BMI ≥ 30	196	53.9	0.81 (0.70, 0.93)	0.80 (0.69, 0.93)	19	4.5	0.68 (0.42, 1.08)	0.67 (0.42, 1.07)
Pivmecillinam, sulfamethizole, nitrofurantoin, trimethoprim, and ciprofloxacin								
BMI < 30 (reference)	2,763	90.0	1	1	649	17.9	1	1
BMI ≥ 30	236	65.8	0.80 (0.70, 0.91)	0.80 (0.70, 0.91)	73	17.6	0.99 (0.78, 1.27)	0.99 (0.78, 1.27)
Pivampicillin, amoxicillin, and amoxicillin + enzyme inhibitor								
BMI < 30 (reference)	783	23.8	1	1	621	17.1	1	1
BMI ≥ 30	130	34.9	1.42 (1.17, 1.71)	1.40 (1.16, 1.69)	106	25.7	1.42 (1.16, 1.75)	1.40 (1.14, 1.73)

Multivariable Cox proportional hazards analysis was performed with BMI ≥ 30 kg/m^2 as predictor.
[a]N: number of cases.
[b]IR: incidence rate per 1000 person-years.
[c]The crude HR was estimated using Cox regression, with age as the underlying time scale.
[d]Multivariable-adjusted model based on the crude model with additional adjustments for current smoking at baseline and comorbidity using Charlson's Comorbidity Index.

based on the calculated BMI as a continuous variable, increasing risk with higher BMI was observed for filled prescriptions overall, phenoxymethylpenicillin, and dicloxacillin/flucloxacillin. A reverse trend was found for the use of pivmecillinam and sulfamethizole among both women and men.

We found no association between obesity and treatment with antifungals and azithromycin.

Similar results were found for waist circumference (see eAppendix Table 2; http://links.lww.com/EDE/A910).

To compare the effect of obesity and current smoking, we performed two additional analyses evaluating the effect of obesity among nonsmoking participants and the effect of current smoking among nonobese participants. The analyses thus share the same reference group, i.e., nonsmoking, nonobese individuals. For men, the association between obesity and infections overall among nonsmoking participants was stronger than the association between current smoking and infections overall among nonobese participants (obesity: women:

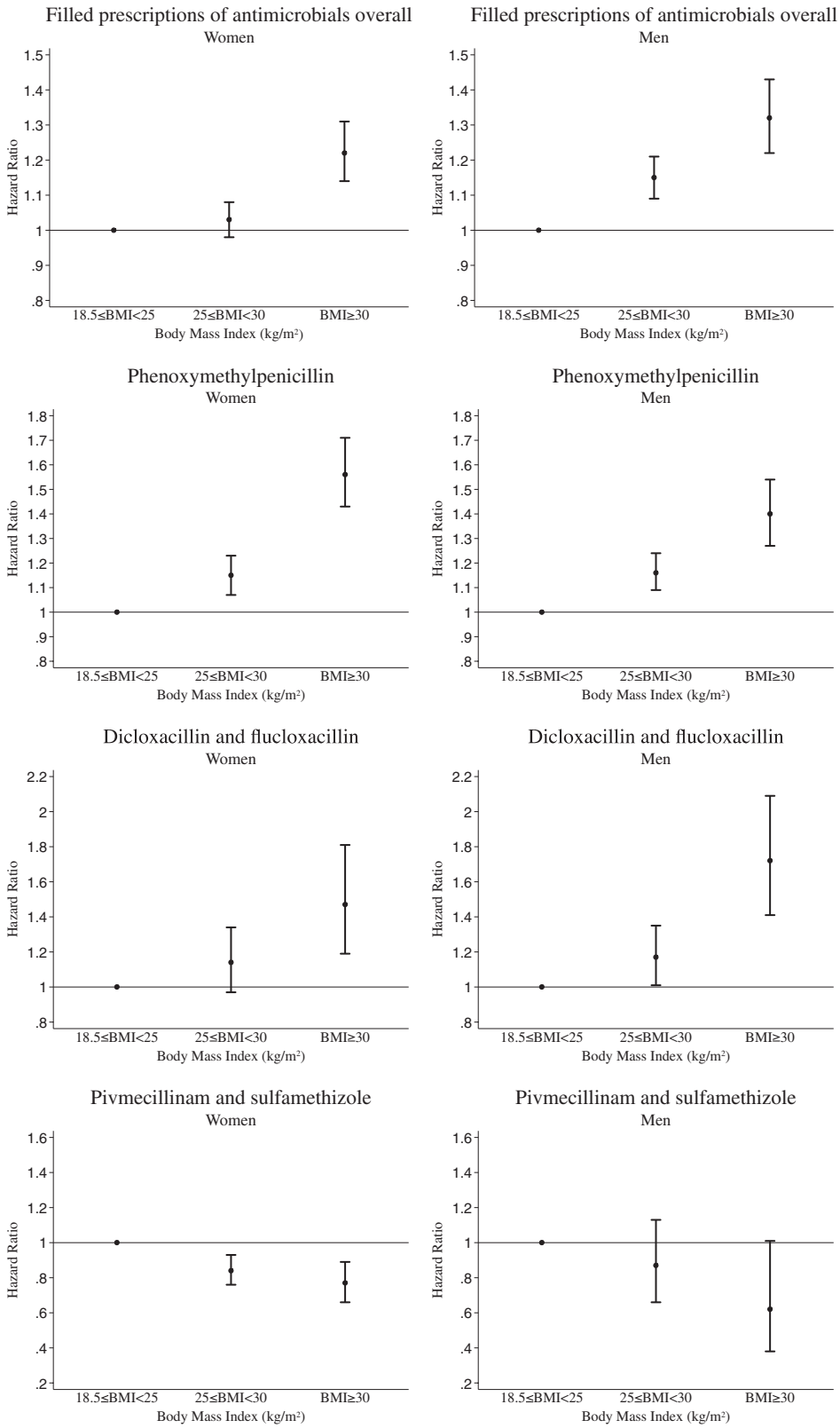

FIGURE 2. The association between BMI strata and filled prescriptions of antimicrobials. Multivariable Cox proportional hazards analysis was performed with BMI strata as predictors, adjusted for smoking status, and comorbidity. Age was used as the underlying timescale. Fewer than 0.7% of the participants were defined as underweight and thus excluded from the analysis. Participants with BMI between 18.5 and 25 were used as reference. *Dots with error bars* Hazard ratios with 95% confidence intervals.

HR = 1.3, 95% CI = 1.0, 1.7; men: HR = 1.5, 95% CI = 1.2, 1.9; smoking: women: HR = 1.2, 95% CI = 1.0, 1.6; men: HR = 1.3, 95% CI = 1.0, 1.5).

DISCUSSION

In this large study of healthy blood donors, obesity was associated with an increased risk of infections. This is the first study to investigate the effect of obesity on the risk of any type of infection among otherwise healthy individuals. In detailed analysis, obesity was most strongly associated with abscesses, infections of the skin and subcutaneous tissue among men, and respiratory tract infections and cystitis among women. Obesity was also associated with an increased risk of filled prescriptions of antimicrobials, both overall and specifically with the use of phenoxymethylpenicillin and macrolides, dicloxacillin and flucloxacillin, and broad-spectrum penicillins. Phenoxymethylpenicillin and the chosen macrolides reflect respiratory tract infections, whereas the indication for dicloxacillin and flucloxacillin is infection with *S. aureus,* which is most often found in skin and subcutaneous tissues. Thus, the findings from analyses with filled prescriptions corroborate the analyses with diagnostic codes as the endpoint.

Overall, the associations changed inconspicuously, when comparing the crude model to the model with adjustments for current smoking status and Charlson's Comorbidity Index.

Only a few studies, to the best of our knowledge, have investigated at the association between obesity and infection in otherwise healthy individuals. A recent Danish study showed a strong association between obesity and risk of hospitalization with pneumonia among men ages 50–64 years.[16] The risk was partly explained by the presence of other chronic diseases in the obese individuals. In another large American study, the impact of confounders was minimized by excluding participants with asthma, cardiovascular diseases, cancer, and diabetes. In this study, obesity and pneumonia were associated in nonhospitalized women.[5]

A large meta-analysis recently found that although obesity (BMI ≥ 30) is associated with higher overall mortality, mortality is lower among overweight individuals (25 ≤ BMI < 30) compared with persons with normal BMI.[23] In contrast, we found an association between overweight and the risk of infection, and the risk was further increased in obese participants.

The explanation for the association between obesity and infection is not obvious, but could be purely anatomical: skin folds and decreased blood perfusion in the peripheral tissues could explain a positive correlation between obesity and especially abscesses and skin infections. Similarly, obesity may cause shallow ventilation, which could facilitate airway infections.

Furthermore, the differences between the observed risk among men and women might be related to the different anatomical constructions.

It is well known that type 2 diabetes, which is highly associated with obesity, affects the immune system and increases the risk of lower respiratory tract infection, urinary tract infection, and skin and mucous membrane infection.[11,24] Individuals with known diabetes are not allowed to donate blood, but blood sugar levels are not measured in the blood banks, so undiagnosed diabetes and impaired fasting glucose among the participants cannot be ruled out. Moreover, obesity alone may alter the immune response. Most immunologic factors produced by adipose tissue are pro-inflammatory and obesity leads to systemic inflammation.[25] We speculate that obesity-induced immune activation lowers the resistance against infection. However, the anatomical explanation presented above is simple and thus may be the most plausible.

Strengths and Limitations of the Study

This study comprised only individuals who were healthy at inclusion, simply because blood donors must comply with strict criteria to be allowed to donate and are permanently excluded from blood donation if diagnosed with certain chronic diseases, including diabetes, cancer, hypertension, or even hypercholesterolemia. Moreover, the participants were followed for a maximum of 2.75 years, so the time at risk for developing comorbidity was short. The short time span minimized the possibility of marked changes in BMI among individual donors. Blood donors lead a healthier lifestyle than the general population.[26] The study population is thus suitable for assessing the impact of obesity on the risk of infection among otherwise healthy individuals.

Obesity is associated with a range of diseases, and ascertainment bias may occur when obese patients are admitted to hospital. The result would be an overestimation of the effect of obesity on the risk of infection. We adjusted for comorbidity using the Charlson's Comorbidity Index, which is a rough measure of comorbidity. Only 3.4% of our study population had an index above 0. In separate analyses with exclusion of participants with an index above 0, only small differences in the HRs were seen. This observation applied to all analyses for the various groups of diagnoses and prescriptions (data not shown).

Moreover, the associations of obesity with treatment for infection at a hospital were corroborated by findings for antimicrobial prescriptions. There was, however, one exception: among women, obesity was associated with an increased risk of cystitis but associated with a decreased risk of filled pivmecillinam and sulfamethizole prescriptions, which is used in treatment of cystitis. The conclusion did not change when the analysis included antimicrobial agents used for complicated urinary tract infection. For approximately 60% of the cystitis cases at hospital, other diagnoses were registered for the same visit, or the patient had other underlying conditions that could explain treatment of cystitis at a hospital. These conditions included pregnancy, childbirth, and urolithiasis.

As a measure of infection, we used ICD-10 codes to identify infection-related treatments at the hospital and ATC

codes to track the use of antimicrobials. Data on the validity of infection-related ICD-10 codes are limited. Validation of the Danish NPR for ICD-10 codes related to infection exists only for a few serious infections, such as pleural empyema.[27]

Although ATC codes mirror the medicine that participants received and serve as a proxy for infection, antimicrobials are often prescribed outside of their proper indication.

We did perform analyses for carbapenems, fluoroquinolones, and cephalosporins, which are broad-spectrum agents that are only used in Denmark under restricted conditions to minimize resistance.[28]

BMI was calculated by self-reported height and weight. Although scales and a measuring-tape were available to participants, some may have measured their weight or waist circumference incorrectly.

CONCLUSION

In a large cohort of healthy individuals, obesity was associated with an increased risk of infections overall and specifically abscesses, infections of the skin and subcutaneous tissue among men, and respiratory tract infections and cystitis among women. The increased risk was similar to the risk associated with the use of antimicrobials overall, and specifically phenoxymethylpenicillin, macrolides, dicloxacillin and flucloxacillin, and broad-spectrum penicillins. The specific mechanisms underlying the associations are not known and need further investigation.

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