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Original Contribution

Body Mass Index and Risk of Infections Among Women in the Danish National Birth Cohort

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We investigated the possible association between body mass index (BMI; weight (kg)/height (m)^2) and hospitalization or treatment for acute infection in a prospective cohort study. We linked 75,001 women enrolled in the Danish National Birth Cohort from 1996 to 2002, who had information on BMI and a broad range of confounders, to data on infectious diseases and use of antimicrobial agents from the National Patient Register and the Danish Prescription Register. Associations were tested using Cox proportional hazards models. During 12 years of follow-up, we observed a U-shaped association between baseline BMI and later hospitalization for 1) any infectious disease and 2) infections of the respiratory tract, whereas a dose-response relationship was seen for skin infections. The most pronounced associations were seen for acute upper respiratory infections at multiple and unspecified sites (underweight (BMI <18.5): hazard ratio (HR) = 4.26, 95% confidence interval (CI): 1.69, 10.7; obesity (BMI ≥30): HR = 3.64, 95% CI: 1.62, 8.18), erysipelas (obesity: HR = 5.19, 95% CI: 3.38, 7.95), and fungal infections (underweight: HR = 3.19, 95% CI: 1.53, 6.66). Slightly greater use of antimicrobials was observed among overweight (BMI 25–<30; HR = 1.08, 95% CI: 1.06, 1.10) and obese (HR = 1.21, 95% CI: 1.17, 1.24) women. Among Danish women, underweight and obesity were associated with increased risk of community-acquired infectious diseases, especially infections of the upper respiratory tract and skin.

antimicrobial agents; body mass index; infections; obesity; underweight

Abbreviations: BMI, body mass index; DNBC, Danish National Birth Cohort; HR, hazard ratio; ICD, *International Classification of Diseases*.

It is well known that the prevalence of obesity has increased worldwide in all age groups (1) and that obesity increases risk of morbidity and mortality through still uncertain pathways (2). Several studies have linked body mass index (BMI; weight (kg)/height (m)^2) with risk of nosocomial and postoperative infections, but the literature on risk of community-acquired infections is still limited (2, 3) and mainly based on small sample sizes or case-control designs or lacking sufficient confounder control. Proposed mechanisms linking BMI and infections involve a decreased cell-mediated immune response, immune system dysregulation, respiratory dysfunction, obesity-related comorbidity, and pharmacological issues (2–4). Among the few studies on community-acquired infections, obesity was found to be associated with greater risk of pneumonia (5), and this may also apply to underweight persons (6–9). Other studies have suggested that obesity protects against mortality from pneumonia (7). Urinary tract and skin infections, including erysipelas (10) and cellulitis (11–15), have also been associated with obesity. For urinary tract infections, the association with obesity is most pronounced in men (16–18), but Kaspersen et al. (19) recently found obesity to be associated with cystitis in women as well. However, Kaspersen et al. did not assess underweight persons and did not differentiate between nosocomial and community-acquired infections; in addition, their study cohort consisted of blood donors, who represent a quite selected population (19). This leaves knowledge on the relationships between both low and high BMI and risk of community-acquired infections contradictory and sparse.

Our aim in the present study was therefore to investigate the possible associations between BMI and risk of community-acquired acute infections using inpatient and outpatient

discharge diagnoses and recorded data on the use of prescribed antimicrobial agents in a large national cohort of younger Danish women. The hypothesis leading to this aim was that both underweight and obesity, through impairment of local and systemic immune responses, may be linked with increased risks of acquiring and clearing a broad spectrum of infections of bacterial, viral, or fungal etiology.

METHODS

Study population

Originally, 91,765 women (corresponding to 100,419 pregnancies) were enrolled in the Danish National Birth Cohort (DNBC) during 1996–2002. The women were recruited in early pregnancy by general practitioners throughout Denmark (more information can be found at www.dnbc.dk). Information from telephone interviews with the participants performed in the 16th (interview 3) and 30th (interview 2) weeks of gestation and 6 months postpartum (interview 3) was used in this study. The cohort consisted of 75,001 women (Figure 1).

Exposure

We used responses to questions concerning height ("How tall are you?") and weight ("What was your weight before the pregnancy?") from interview 1 to calculate prepregnancy BMI. The BMI ranges used were based on the international World Health Organization classification, where BMI <18.5 is considered underweight, BMI 18.5–<25 is normal weight (referent), BMI 25–<30 is overweight, and BMI ≥30 is obese (20).

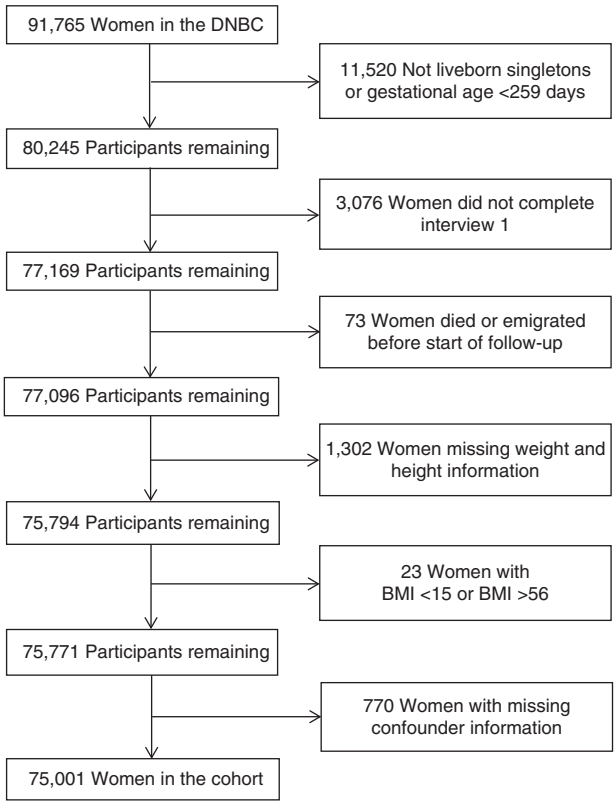

Figure 1. Selection of women from the Danish National Birth Cohort (DNBC) for the current study, Denmark, 1996–2012. BMI, body mass index (weight (kg)/height $(m)^2$).

Outcomes

Information on diagnoses of community-acquired infectious diseases was obtained from the Danish National Patient Register (21) using codes from the *International Classification of Diseases* (ICD), *Tenth Revision* (ICD-10). Primary hospital admission diagnoses, each counting as an inpatient or outpatient hospital contact, were included (see Web Table 1, available at http://aje.oxfordjournals.org/). In Denmark, the majority of milder infectious diseases are treated not in a hospital but by a general practitioner. Thus, in order to obtain complete information on the incidence of infectious diseases among cohort participants, we used the Danish Prescription Register (22) to collect information on use of antimicrobial agents, 90% of which are prescribed by general practitioners in Denmark (23). The antibacterial and antifungal agents were divided into organ-specific groups according to their presumed indication (similar to Latour et al. (24)) and included suspected infections of the respiratory tract, skin, and urinary tract and gynecological/abdominal locations (Web Table 2 shows the antimicrobials included in each group). Antimicrobials used for treating infections in more than 1 specific organ group were not included in the organ-specific categorization. The linkage between cohort members and registers was possible because of the unique 10-digit personal identification number given to all Danish citizens at birth (25).

Covariates

Information about a priori confounders was obtained from the DNBC and included parity at the time of pregnancy, ever smoking (smoking during and/or after pregnancy reported in interview 1, 2, and/or 3 vs. no smoking reported in any of the interviews), alcohol consumption (units/week; 1 unit = 12 g of pure ethanol) prior to pregnancy, exercise during pregnancy (as a proxy for general physical activity), and sociooccupational status at pregnancy (based on the woman's current or most recent occupation within the last 6 months or, if the woman was in school, on type of education post–primary school; women who could not be classified in this way were categorized according to their husband's sociooccupational status; variable defined previously (26)).

We adjusted for certain chronic diseases (9 variables categorized as yes/no) suggested to be associated with BMI as well as infectious diseases. These included lung disease (including asthma and chronic obstructive lung disease), hypertension, ischemic heart disease, dyslipidemia, chronic renal disease, diabetes mellitus (type 1, type 2, and gestational), chronic skin ulcers, malignant neoplasms, and human immunodeficiency virus infection. Information on these diseases was obtained from the Danish National Patient Register (*International Classification of Diseases, Eighth Revision* (ICD-8) and ICD-10 codes) and from the Danish Prescription Register (Anatomical-Therapeutic-Chemical codes); at least

Table 1. Characteristics of Women From the Danish National Birth Cohort Selected for a Study of Body Mass Index and Infection Risk ($n = 75{,}001$), Denmark, 1996–2012

Characteristic	No. of Women	%
Start of Follow Up		
Age, years[a]	30.7 (27.9–33.8)	
Parity prior to pregnancy		
0	36,988	49.3
1	26,195	34.9
≥2	11,818	15.8
Prepregnancy alcohol consumption, units[b]/week		
0	9,440	12.6
1–7	57,978	77.3
≥8	7,583	10.1
Smoking (ever, during pregnancy, or after pregnancy)		
No smoking reported in interview 1, 2, or 3	54,321	72.4
Any smoking reported in interview 1, 2, or 3	20,680	27.6
Socio-occupational status during pregnancy		
Long (>4 years) PPS education/leader in large company	15,687	20.9
Middle-long (3–4 years) PPS education/ leader in small company	23,902	31.9
Short (<3 years) PPS education/ vocational/still in school	28,344	37.8
Unskilled/other work/unemployment benefits	5,467	7.3
On state welfare	1,601	2.1
Prepregnancy body mass index[c]		
<18.5	3,323	4.4
18.5–24.9	51,135	68.2
25–29.9	14,476	19.3
≥30	6,067	8.1
Body mass index 6 months after delivery		
<18.5	2,086	2.8
18.5–24.9	35,873	47.8
25–29.9	13,434	17.9
≥30	5,090	6.8
Missing data	18,518	24.7
Exercise during pregnancy, minutes/week		
No exercise	46,929	62.6
1–<120	15,373	20.5
120–<240	8,451	11.3
240–<420	3,112	4.1
≥420	1,136	1.5
End of Follow-up		
Chronic disease		
Chronic lung disease	14,446	19.3
Ischemic heart disease	660	0.9
Hypertension	6,274	8.4
Dyslipidemia	1,516	2.0
Chronic renal disease	160	0.2
Diabetes mellitus (type 1, type 2, or gestational)	2,437	3.2
Chronic skin ulcers	43	0.1
Malignant neoplasms	2,327	3.1
Human immunodeficiency virus infection	5	0.0

Abbreviation: PPS, post–primary school.
[a] Value is presented as median (interquartile range).
[b] 1 unit = 12 g of pure ethanol.
[c] Weight (kg)/height $(m)^2$.

Table continues

2 consecutive prescriptions (assumed average daily maintenance dose) or at least 3 different prescriptions for the same drug were required to identify the presence of a specific disease. In both cases, the first prescription had to be registered before the outcome date. Unfilled prescriptions were not included. Self-reported information about physician-diagnosed asthma and diabetes mellitus from interview 1 was included in the chronic lung disease and diabetes groups, respectively. Details on the chosen ICD and Anatomical-Therapeutic-Chemical codes and the DNBC questions are displayed in Web Table 3. Note that azithromycin was not included as a gynecological or respiratory antimicrobial, since it was not possible to determine the indication for its use.

Statistical analysis

We investigated the possible associations between BMI and risk of infections by calculating hazard ratios and 95% confidence intervals using Cox regression, with the woman's age as the underlying time scale. For hospital contacts with infectious diseases, women were followed from 6 months postpartum onward, unless this date occurred less than 30 days before the latest discharge date. In that case, follow-up started 30 days after this hospital contact. For antimicrobials, follow-up also started 6 months postpartum, and if this date occurred less than 30 days after a prescription, follow-up started at the end of this period. A minimum of 30 days between 2 prescriptions was required for the second to count as a new prescription. Women were followed to the development of infectious disease (first hospital contact, determined using primary inpatient and outpatient diagnoses and excluding emergency room contacts because they are assumed to be less credible) or the first episode of prescribed antimicrobial medication, emigration, death, or the end of follow-up (December 31, 2012). Women were followed until their first hospital contact for a specific infection (disregarding other infections) or their first antimicrobial prescription (disregarding previous prescriptions included in other categories). An exception was the category "any infection/antimicrobial," where only the first infectious disease diagnosis or prescribed

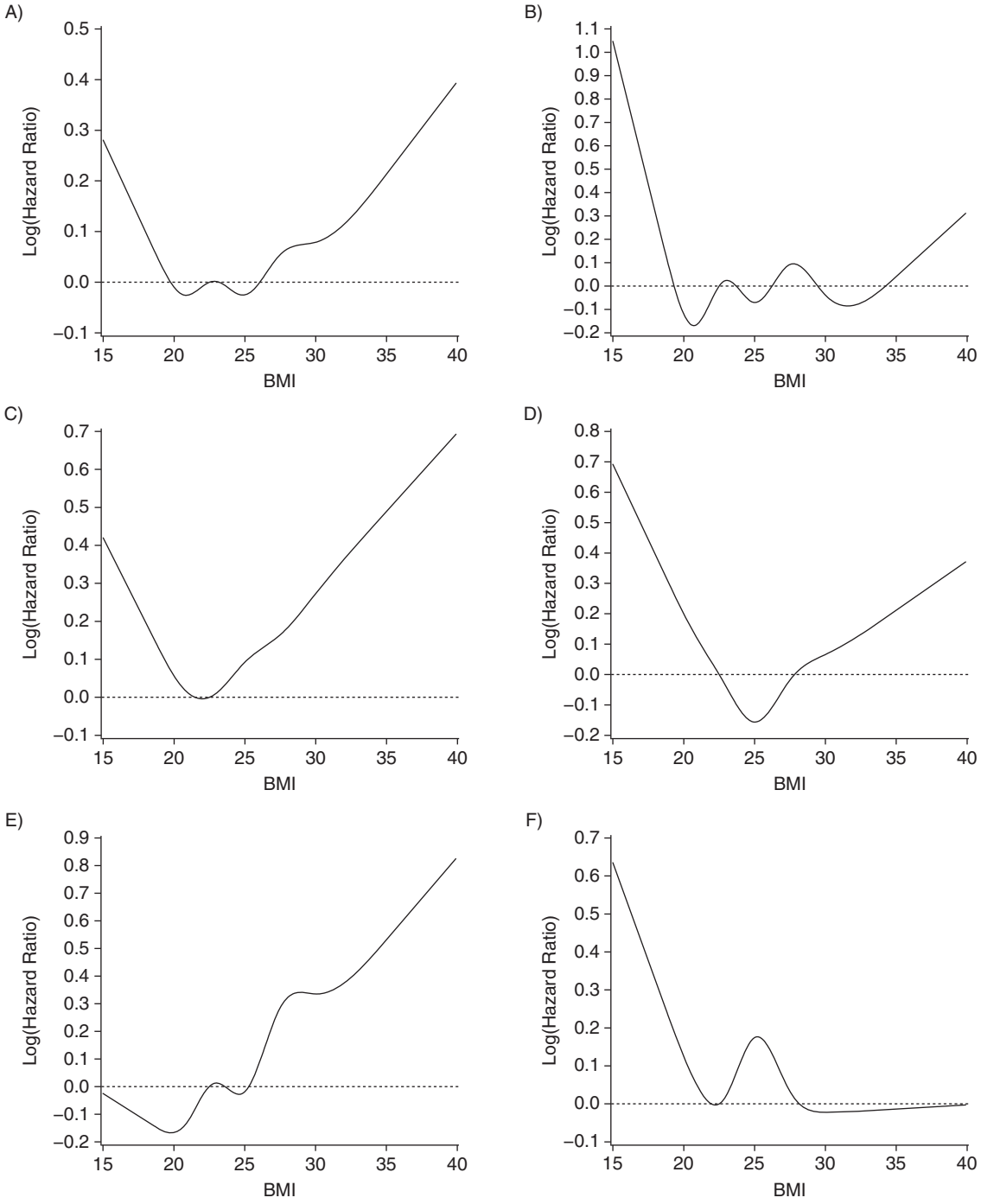

Figure 2. Hazard ratios for infectious disease hospitalization according to body mass index (BMI; weight (kg)/height (m)^2) for the main groups of infections showing significant associations with BMI, Denmark, 1996–2012. Per the World Health Organization classification (20), underweight was defined as BMI <18.5, normal weight as BMI 18.5–24.9 (referent), overweight as BMI 25–29.9, and obesity as BMI ≥30. A) Any infection (n = 6,916); B) gastrointestinal tract infection (n = 817); C) upper respiratory tract infection (n = 1,251); D) lower respiratory tract infection (n = 1,255); E) skin and subcutaneous tissue infection (n = 1,287); F) urinary tract infection (n = 687).

antimicrobial agent was included. Thus, repeated hospital contacts for the same infection were not allowed in any analysis.

Primary diagnoses describing the main cause of hospital contact were used to avoid nosocomial infections, and chronic infections were not included in the study. For the overall disease groups (any infection, gastrointestinal infection, respiratory infection, urinary tract infection, and skin infection), splines were constructed to visualize hazard ratios

Table 2. Adjusted[a] Hazard Ratios for Infectious Disease Requiring Hospital Contact or Prescribed Antimicrobial Agents, According to Body Mass Index,[b] Denmark, 1996–2012

Infection or Antimicrobial Agent	Person-Years at Risk	No. of Cases	BMI Category								*P* Value[c]
			<18.5		18.5–24.9		25–29.9		≥30		
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	
Infections											
Any infection	831,625	6,916	1.13	1.01, 1.26	1	Referent	1.03	0.97, 1.09	1.22	1.12, 1.32	<0.01
Respiratory tract	862,334	2,444	1.30	1.09, 1.54	1	Referent	1.00	0.91, 1.12	1.29	1.13, 1.47	<0.01
Gastrointestinal tract	881,707	817	1.48	1.11, 1.96	1	Referent	1.08	0.91, 1.29	1.16	0.92, 1.47	0.04
Skin and subcutaneous tissue	879,140	1,287	1.02	0.78, 1.33	1	Referent	1.27	1.11, 1.46	1.78	1.50, 2.10	<0.01
Urinary tract	883,147	687	1.51	1.12, 2.03	1	Referent	1.03	0.85, 1.25	0.93	0.71, 1.24	0.04
Circulatory system	887,031	56	1.88	0.74, 4.82	1	Referent	0.44	0.19, 1.06	0.56	0.17, 1.88	0.10
Nervous system	886,109	170	1.43	0.76, 2.66	1	Referent	1.08	0.74, 1.59	0.82	0.45, 1.52	0.60
Gynecological infection	878,180	1,219	0.78	0.59, 1.03	1	Referent	0.87	0.74, 1.01	0.96	0.79, 1.18	0.11
Influenza	886,735	88	1.56	0.67, 3.64	1	Referent	0.70	0.38, 1.29	1.31	0.67, 2.56	0.30
Sepsis	886,541	147	0.93	0.40, 2.13	1	Referent	1.16	0.77, 1.74	1.03	0.58, 1.85	0.91
Other	881,961	866	1.14	0.83, 1.56	1	Referent	1.08	0.91, 1.28	1.06	0.83, 1.35	0.73
Antimicrobial agents											
Any antimicrobial agent	177,445	71,896	0.97	0.94, 1.01	1	Referent	1.06	1.04, 1.08	1.16	1.13, 1.20	<0.01
ATC coding group											
Antibacterials	196,334	71,062	0.99	0.95, 1.02	1	Referent	1.08	1.06, 1.10	1.21	1.17, 1.24	<0.01
Antifungals	688,376	26,656	0.94	0.88, 1.00	1	Referent	0.92	0.89, 0.95	0.92	0.87, 0.96	<0.01
Antivirals	834,158	8,906	1.05	0.95, 1.15	1	Referent	0.83	0.78, 0.88	0.81	0.74, 0.88	<0.01
Antimycobacterials	887,160	36	1.15	0.27, 4.93	1	Referent	0.75	0.30, 1.86	0.85	0.27, 2.67	0.92
Organ-specific groups											
Respiratory tract	271,294	66,414	0.97	0.93, 1.01	1	Referent	1.10	1.08, 1.13	1.28	1.24, 1.31	<0.01
Skin	767,702	18,548	0.93	0.87, 1.00	1	Referent	1.12	1.08, 1.16	1.27	1.21, 1.34	<0.01
Gynecological/abdominal organs	698,978	25,505	0.93	0.88, 0.99	1	Referent	0.91	0.88, 0.94	0.92	0.88, 0.96	<0.01
Urinary tract	652,261	32,525	1.05	0.99, 1.10	1	Referent	1.00	0.97, 1.03	1.08	1.04, 1.13	<0.01

Abbreviations: ATC, Anatomical-Therapeutic-Chemical; BMI, body mass index; CI, confidence interval; HR, hazard ratio.
[a] Adjusted for smoking, alcohol, parity, socio-occupational status, exercise, and chronic diseases.
[b] Weight (kg)/height $(m)^2$.
[c] Test of homogeneity by BMI using the 4 BMI categories.

according to BMI (knot points at BMIs of 18.5, 20.7, 22.8, 25, 27.5, 30, and 35; referent, BMI 22.5). No interaction between BMI and chronic diseases was found. Tests for homogeneity of hazard ratios by BMI were performed using the 4 BMI categories, and *P* values less than 0.05 were considered significant. The empirical score process (27) was used to evaluate the proportional hazards assumption; no violation of the assumption was found. All statistics were evaluated by means of Wald tests using SAS software, versions 9.3 and 9.4 (updated during study period; SAS Institute, Inc., Cary, North Carolina).

Ethical considerations

The study was purely register- and questionnaire-based, without contact with study participants. The study protocol followed the regulations and instructions set up by the Danish Data Protection Agency.

RESULTS

The 75,001 women in the cohort had a median age of 30.7 years at study entry and were followed for a median of 11.9 years (interquartile range, 10.7–13.0). The most common of the included chronic diseases were chronic lung disease and hypertension at the end of follow-up. During the follow-up period, 9.6% of participants had hospital contact due to an infection, and 95.9% received antimicrobial agents. Other characteristics are shown in Table 1.

Results are presented as splines (Figure 2), adjusted hazard ratios for the main disease groups (Table 2), and adjusted hazard ratios for subgroups associated with BMI (Table 3). Crude hazard ratios, which showed the same pattern as adjusted hazard ratios, and hazard ratios for subgroups of infections not associated with BMI are shown in Web Tables 4–6. Risk of any infection was U-shaped, with higher risks in both underweight and obese women

Table 3. Adjusted[a] Hazard Ratios for Significant Subgroups of Infectious Diseases Requiring Hospital Contact, According to Body Mass Index,[b] Denmark, 1996–2012

Location and Type of Infection	No. of Cases	BMI Category								*P* Value[c]
		<18.5		18.5–24.9		25–29.9		≥30		
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	
Respiratory tract										
URTI	1,251	1.21	0.95, 1.55	1	Referent	1.12	0.97, 1.30	1.48	1.23, 1.78	<0.01
URTI at multiple sites[d]	41	4.26	1.69, 10.7	1	Referent	0.80	0.30, 2.14	3.64	1.62, 8.18	<0.01
Sinusitis	128	2.34	1.29, 4.25	1	Referent	0.87	0.53, 1.43	1.68	0.97, 2.92	<0.01
Tonsillitis	420	0.91	0.56, 1.47	1	Referent	1.23	0.97, 1.56	1.73	1.28, 2.33	<0.01
LRTI	1,255	1.34	1.06, 1.69	1	Referent	0.88	0.76, 1.03	1.12	0.92, 1.35	<0.01
Pneumonia	1,109	1.33	1.04, 1.70	1	Referent	0.84	0.72, 0.99	1.08	0.88, 1.32	<0.01
Gastrointestinal tract										
Intestinal infectious disease	816	1.48	1.11, 1.96	1	Referent	1.08	0.91, 1.29	1.15	0.90, 1.45	0.05
Skin and subcutaneous tissue										
Acute lymphadenitis	94	2.44	1.24, 4.80	1	Referent	0.82	0.45, 1.47	1.35	0.67, 2.69	0.04
Cellulitis and abscess	761	0.80	0.55, 1.16	1	Referent	1.29	1.08, 1.53	1.64	1.32, 2.05	<0.01
Erysipelas	141	2.03	0.97, 4.27	1	Referent	1.84	1.19, 2.83	5.19	3.38, 7.95	<0.01
Pilonidal cyst	121	0.32	0.08, 1.33	1	Referent	1.68	1.11, 2.54	1.67	0.96, 2.90	0.01
Other skin infection	99	1.79	0.81, 3.98	1	Referent	1.56	0.96, 2.55	2.16	1.20, 3.89	0.04
Nervous system										
Encephalitis	48	2.79	1.06, 7.35	1	Referent	2.22	1.18, 4.20	0.63	0.14, 2.75	0.02
Gynecological organs										
Cervicitis uteri	103	0.56	0.18, 1.79	1	Referent	0.58	0.32, 1.04	1.60	0.92, 2.80	0.04
Other infections										
Other fungal infection	62	3.19	1.53, 6.66	1	Referent	0.98	0.51, 1.90	0.34	0.08, 1.46	<0.01

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

[a] Adjusted for smoking, alcohol, parity, socio-occupational status, exercise, and chronic diseases.

[b] Weight (kg)/height $(m)^2$.

[c] Tests of homogeneity by BMI using the 4 BMI categories.

[d] Acute URTI at multiple and unspecified sites.

after adjustment for chronic diseases and other potential confounders (Table 2 and Figure 2A). The U-shaped pattern was also seen for infections of the respiratory tract and (less pronounced) the gastrointestinal tract (Figure 2B–D). Risk of encephalitis seemed to be increased in both underweight and overweight women but not obese women (Table 3), with the majority of cases diagnosed as unspecified encephalitis. Overweight and obesity per se were associated with upper respiratory tract infections overall, including tonsillitis, and with infections of the skin and subcutaneous tissue, including cellulitis and abscess, erysipelas, pilonidal cyst, and other skin- and subcutaneous tissue-related infections (Table 3 and Figure 2E). Among underweight women, increased risks of intestinal infectious diseases, sinusitis, lower respiratory tract infections overall (including pneumonia), urinary tract infections overall, acute lymphadenitis, and fungal infections were observed (Tables 2 and 3 and Figure 2F). Overweight women were at slightly lower risk of pneumonia. The most pronounced associations, with more than 2-fold higher risks, were found for acute upper respiratory infections at multiple and unspecified sites (underweight, >4-fold; obesity, >3-fold), sinusitis (underweight, >2-fold), acute lymphadenitis (underweight, >2-fold), erysipelas (obesity, >5-fold), other infections of the skin and subcutaneous tissue (obesity, >2-fold), and fungal infections (underweight, >3-fold) (see Table 3).

Greater use of antimicrobial agents overall was observed in overweight and obese women, mainly driven by use of antibacterials. On the other hand, overweight and obese women were at slightly lower risk of being prescribed antifungals and antivirals. Among overweight and obese women, greater use of antimicrobials was observed for respiratory tract and skin infections. In addition, risk of treatment for urinary tract infections tended to be higher among obese women as well as underweight women. In contrast, antimicrobials for gynecological/abdominal infections were prescribed marginally less frequently to underweight, overweight, and obese women (Table 2).

Sensitivity and robustness

Details on analyses of sensitivity and robustness are presented in Web Tables 7–14. BMI 6 months after birth showed

the same pattern (Web Tables 7–10) and had a similar distribution across BMI categories (Table 1) as prepregnancy BMI. Including gestational weight gain in the adjustment did not change the associations markedly (Web Tables 11–14). Risk of all fungal infections (as opposed to "other fungal infections," where only fungal infections not included in other specific groups were represented) was higher in underweight women, and risk of opportunistic infections was not associated with BMI. When we assessed a single prescription versus 1 or more prescriptions, estimates did not change markedly. For respiratory tract and skin infections, obese women were at increased risk of receiving more than 1 prescription per infection, while no association between length of hospital stay (in days) and BMI was found. Further, results did not seem to be affected by birth complications during the first 6–12 months after delivery. Comorbidity, including diabetes, did not influence the findings markedly.

DISCUSSION

Overall, a U-shaped relationship was found between BMI and risk of hospital-diagnosed acute community-acquired infections in younger Danish women, pointing to increased susceptibility to infections in both underweight and overweight women. This pattern was especially observed for upper respiratory tract infections. Risk of skin infections showed a dose-response relationship with increasing BMI, and underweight was associated with an elevated risk of fungal and urinary tract infections. While data suggested that treatment for respiratory and skin infections was associated with obesity, risk of treatment with antiviral and antifungal agents was lower in overweight and obese women.

A major strength of this study is that it was the first study, to our knowledge, to investigate associations between both high and low BMI and risk of a broad spectrum of physician-verified community-acquired infectious diseases and antimicrobial treatment in a large cohort followed for more than a decade, with detailed information on potential confounders, including comorbid conditions. We were thereby capable of capturing both more severe infections requiring contact with hospital settings and infections treated by general practitioners, though misdiagnosis should be considered, especially in general practice. Further, BMI was reported at the start of follow-up, before disease development, hence minimizing recall bias.

As to limitations, BMI is a controversial measure of body fat in comparison with waist circumference, waist:hip ratio, and dual-energy x-ray absorptiometry. However, BMI and fat mass have been found highly correlated ($r = 0.94$) (28) and to correspond fairly well with overall percentage of body fat within sex-age groups (29). Prepregnancy BMI was used as the primary measure of BMI, and weight was suggested to increase equally for most BMI categories from early adulthood (ages 25–33 years) on and from age 18 years on in a previous study (30).

In general, weight is likely to be underreported by women, particularly those with high BMI, whereas height tends to be overreported (31). Nonetheless, self-reported weight and height have been investigated specifically in pregnant women and women of reproductive age, and self-reported prepregnancy BMI has generally been found to be reliable for research purposes (32, 33). To further investigate the potential bias in using self-reported weight and height, these data were previously validated among 5,033 participants in the DNBC (26). The risk estimates based on self-reported BMI were expected to be underestimated only by approximately 5%. Further, the body weights of all Danish women are closely monitored throughout pregnancy, and the private records are kept by the women after birth. Overall, the reporting bias due to self-reported BMI is assumed to be minor. Besides, we found similar results using BMI 6 months postpartum as the exposure, and additional adjustment for gestational weight gain did not change the results. In the analyses using information from the Danish National Patient Register, milder infections not requiring hospital contact were not captured. While the results were in accordance with our analyses of antimicrobial use, reflecting infections treated outside of hospital settings, it must be borne in mind that viral infections, especially, are often not medically treated and will be missed.

The accuracy of the Danish National Patient Register has previously been validated for community-acquired infections overall, with a positive likelihood ratio decreasing with older age, severe comorbidity, and the presence of immunosuppression (34). In our study, however, the cohort comprised younger, healthy women, thereby minimizing the risk of differential misclassification. High or low BMI may lead to greater use of health-care services at a young age (35) due to increased morbidity requiring medical attention; therefore, such women might be more likely to be registered as having filled at least 1 prescription, which in turn may be a source of ascertainment bias. However, in our study, the bias may apply mostly for the antimicrobials, since hospital admissions due to infections were acute and should not have depended on medical-care-seeking behavior. A possible source of selection bias was that women of low socio-occupational status are underrepresented in the DNBC (36). Compared with the general population, members of the DNBC have been found to be somewhat healthier in terms of weight and smoking; however, odds ratios for 3 different associations, including BMI and stillbirth risk, were not biased by nonparticipation in the DNBC (37). Finally, our findings should not be considered representative of women in general but apply to younger women of reproductive age in Western countries, where exposure to some infections (such as tuberculosis) is very limited and for which data were therefore not included in the present study.

A potential U- or J-shaped relationship between BMI and infections was described in a previous review (4), which is in accord with the findings for at least some of the infections investigated in the present study. Recently, Wang et al. (38) found obesity to be related to use of antibiotics among men with chronic diseases, but the information was based solely on self-reports and the authors did not categorize the antibiotics given any further. Obesity has been associated with defects in upper airway neuromechanical control (39), which could lead to increased susceptibility to upper respiratory infections due to chronic inflammation in the respiratory tract, also seen in persons with obstructive sleep apnea (2). In support of our results from both in-hospital and outside-hospital settings, Campitelli et al. (40) recently found a U-shaped association between BMI and assumed community-acquired acute respiratory infections during non-influenza-season

periods. They did not differentiate between specific upper and lower respiratory tract infections as we did in our study, and in general, few studies in the field exist. With regard to sinusitis, where we found an indication of increased risk in obese women, a previous study suggested a higher prevalence of obesity in adults with chronic rhinosinusitis (41). That study suggests that the inflammation seen in both obesity and sinusitis might be the link, and this may also be a possible explanation for our findings, as well as for the increased risk of tonsillitis in obese women. In a recent review, Torres et al. (42) concluded that risk of community-acquired pneumonia is higher in underweight persons, reduced in overweight persons, and either lower or the same in obese persons as in normal-weight persons. This is in line with the findings of this study, strengthening the validity of the results. Studies have even found obesity to protect against 30-day mortality from community-acquired pneumonia (43, 44). In a recent Danish cohort study among blood donors, Kaspersen et al. (19) found obesity to be associated with greater risk of pneumonia on the basis of 15 observed cases among women, as opposed to 115 cases in our study.

Data on the association between low BMI and risk of intestinal infections has not been presented in previous publications, to our knowledge. The finding of underweight women's being at risk of acute intestinal infections may have been due to malnutrition, comorbidity (although several chronic diseases were accounted for in adjustments), and/or an influence on the immune system as described below. The latter explanation may also be applicable to the increasing risk of intestinal infections with more extreme (high) BMI values seen in the splines, although this association was not observed by Kaspersen et al. (19), possibly because of a lack of statistical power (only 3 cases of infectious gastrointestinal diseases in the obese category as compared with 85 in our study).

A greater risk of skin infections has been found among obese persons in several case-control studies (10–12, 14, 15) and among Danish blood donors (19); but, to our knowledge, this is the first cohort study in the field including both low and high BMI that also included erysipelas (missing for women in the Danish blood donor study). Thus, our robust results support previous findings, and they show a dose-response relationship with BMI, especially for erysipelas/cellulitis, where the risk was found to be 5-fold higher among obese women. These findings were supported by our results on the use of antimicrobials for skin infections, increasing their validity, since many skin infections are treated outside of hospital settings. We based the diagnosis of cellulitis and erysipelas on ICD-10 codes, but differentiation between the two diagnoses varies because of intercountry differences (13) and a wide range of possible tissue involvement (45). Probable explanations such as venous insufficiency, impaired lymphatic flow, greater skin fragility, and lower hygiene levels have been suggested (13).

In support of our findings showing a tendency toward increased risk in underweight women as observed in the splines, Geerlings et al. (46) found low BMI in diabetic women to be associated with risk of urinary tract infections. However, this could not be replicated in our analyses of the use of antimicrobials for treatment of urinary tract infections. Other studies solely investigated possible associations between obesity and urinary tract infections and found an association mainly in men (16–18), possibly caused by a higher prostate volume in obesity. Contrarily, Kaspersen et al. (19) found obese women to be at risk of urinary tract infections, which was slightly supported by our analyses of the use of antimicrobials against urinary tract infections; however, the inclusion of nosocomial infections in the previous study leaves the cause of infection (i.e., obesity vs. hospitalization) uncertain.

We found no association between BMI and more severe outcomes such as sepsis, as suggested in a previous study by Wang et al. (47), but risk of encephalitis seemed increased among both underweight and overweight women. The low number of cases in this category ($n = 2$) probably explains why obese women did not seem to be at risk of encephalitis. Most of the encephalitis cases were of unspecified origin and were not cases of herpes encephalitis, which might have been expected if excess risk among underweight women was due to immunosuppression. To our knowledge, no previous studies have investigated the relationship between body composition and risk of community-acquired fungal infections overall. We found a higher risk among underweight women in general but no increased risk of infections among persons with diabetes (compared with nondiabetics), supporting the validity of our results.

In this study, we found an increased risk of contracting some infections among both underweight and obese women. Obesity has been shown to alter the pharmacokinetics and pharmacodynamics of antimicrobial agents (3). Previous studies have indicated that underdosing in obese persons is common (3), and for underweight persons, antibiotic overdosage and toxicity might pose a problem (4). Further, reflecting the chronic inflammation caused by obesity (recently termed meta-inflammation (48)), with elevated levels of adipokines, C-reactive protein, and other cytokines (49), obesity has been suggested to cause leptin resistance (50–52). This may lead to increased vulnerability to infections, since leptin signaling in the central nervous system has been shown to be essential for an optimal immune response (50–52). Leptin levels have been found to be low in underweight persons (4), giving rise to the same lack of an appropriate immune response.

In conclusion, we found a U-shaped association between BMI and risk of infections requiring hospital contact, particularly acute upper respiratory tract infections. Underweight women were found to be more prone to urinary tract and fungal infections, whereas obese women were at greater risk of skin infections. Further, obese women were at higher risk of being treated with antimicrobial agents for bacterial infections but at slightly lower risk of being treated with antimicrobials for medically treatable viral and fungal infections. These results may reflect the influence of inflammation on the immune system, caused by a lack or excess of adipose tissue, and thereby greater vulnerability to infections.

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