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Original Article

Body mass index and the incidence of influenza-associated pneumonia in a UK primary care cohort

William A. Blumentals,[a] Alan Nevitt,[b] Michael M. Peng,[a] Stephen Toovey[c]

[a]Hoffmann-La Roche, Inc., Nutley, NJ, USA. [b]F. Hoffmann-La Roche Ltd, Basel, Switzerland. [c]Royal Free and University College Medical School, London, UK.

Correspondence: William A. Blumentals, PhD, Epidemiology, Patient-Reported Outcomes & Healthcare Data Strategy, Hoffmann-La Roche, Inc., Building 1/6A28, 340 Kingsland Street, Nutley, NJ 07110, USA. E-mail: william.blumentals@roche.com

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Background Accumulating data suggest an association between increased BMI/obesity and morbidity in patients with pandemic (H1N1) 2009 influenza. Information on metabolic status and prognosis in seasonal influenza is lacking, however.

Methods A retrospective cohort study was carried out using the UK General Practice Research Database. Patients aged ≥18 with ≥1 recorded BMI in the 12–58 kg/m^2 range between January 1, 2000, and December 31, 2007, were observed for an influenza-associated pneumonia diagnosis after the date of baseline BMI, including 'influenza with pneumonia' or a diagnosis of 'pneumonia' up to 30 days after a diagnosis of 'influenza'.

Results A total of 1 074 315 patients were included, of whom 73·2% were within the reference BMI range or overweight and 2·2% were underweight (<18·5 kg/m^2). Pneumonia rates were 32·33–37·48/100 000 in all BMI categories except the underweight (98·29/100 000). Relative to patients with acceptable weight, those who were underweight had an increased pneumonia rate [adjusted IRR = 2·32 (95% CI 1·80–2·94)], while being overweight (BMI = 25·0–29·9 kg/m^2) or obese (BMI ≥ 30·0 kg/m^2) was associated with a decreased pneumonia rate [adjusted IRR = 0·77 (95% CI 0·68–0·86) and 0·85 (95% CI 0·73–1·00), respectively]. On the other hand, women and obese women with type 2 diabetes had increased pneumonia rates [adjusted IRR = 1·37 (95% CI 1·08–1·72) and 1·47 (95%CI 1·01–2·06), respectively].

Conclusions In contrast to initial data from pandemic influenza, influenza pneumonia, and pneumonia following influenza were the most common in underweight persons, and an apparent decreased rate of pneumonia was noted with increasing BMI categories. Women with type 2 diabetes had increased rates of pneumonia.

Keywords Body mass index, obesity, pneumonia, risk factors, seasonal influenza, type 2 diabetes.

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Introduction

In April 2009, a novel influenza A (H1N1) virus of swine origin emerged in Mexico.[1] This virus is antigenically and genetically unrelated to human seasonal influenza viruses and has since spread across the world. As of August 1, 2010, more than 214 countries and overseas territories/communities had reported confirmed cases of pandemic influenza A (H1N1) 2009. These cases included over 18 449 deaths.[2] The characteristics of patients becoming critically ill and/or dying from pandemic (H1N1) 2009 influenza have been studied extensively since the emergence of the outbreak.[3–7] Some authors have suggested an apparent association between high body mass index (BMI)/obesity and increased severity of disease, complications, or death in patients with pandemic influenza (as opposed to influenza in general). Obesity has been cited as a common comorbidity in critically ill patients with pandemic influenza in intensive care units (ICUs) in Canada[7] and Mexico[5] and in ICU patients in the state of Michigan, USA.[4] In their sample of 168 critically ill patients with pandemic (H1N1) 2009 influenza in centers across Canada, Kumar *et al.* found 33% to be obese, a higher proportion than the approximate 24% reported for the Canadian general population.[7] Increased BMI was not linked to reduced likelihood of survival, however. Similarly, data obtained from six Mexican hospitals showed obesity to be the most common comorbidity in 58 critically ill patients with pandemic influenza (36% prevalence compared with 30% in the general population), but with no association between BMI and survival.[5]

Other studies have suggested the possibility of an association between obesity and an increase in mortality in patients with pandemic (H1N1) 2009 influenza. Of 10 patients admitted to Michigan ICUs for acute respiratory distress syndrome secondary to this strain of influenza A, nine were obese, seven had BMI ≥40, and three patients died.[4] The Centers for Disease Control highlighted the potential for severe complications of novel influenza A (H1N1), particularly in extremely obese patients.[4] The possibility of a link between obesity and mortality in patients with pandemic (H1N1) 2009 influenza has been explored further in the multinational setting by a French group examining 574 deaths up to mid-July 2009.[8] Pregnancy and 'metabolic condition' (which included obesity and diabetes) were highlighted as risk factors of particular importance. Of 13 patients with sufficient data who died, seven were obese.

The 2009 strain of pandemic influenza A (H1N1) should be contrasted with seasonal influenza, the effects of which are felt globally every year when the disease develops in around 20% of the world's population overall.[9] Seasonal influenza results in significant hospitalization rates and morbidity in adults and children, which translates into a substantial economic burden. The total direct annual cost of influenza in the USA has been estimated at US$1–3 billion and the indirect cost (representing lost productivity) at US$10–15 billion.[10] Despite this, the economic impact of influenza is often underestimated, possibly because of the perception that the disease is self-limiting and will respond to bed rest and symptomatic treatment.[10]

Relative to pandemic influenza, there is very little information on the effect of metabolic status on prognosis or incidence of complications in patients with seasonal influenza. The objective of the current study was to attempt to address this issue using data gathered over 8 years to study the effect of BMI on the incidence of influenza-associated pneumonia in patients included in a large national UK database.

Methods

Study design

This was a retrospective cohort study conducted in patients included in the UK General Practice Research Database (GPRD) from January 1, 2000, to December 31, 2007, a period that preceded the appearance of the pandemic (H1N1) 2009 virus. The UK GPRD is the world's largest computerized database of anonymized longitudinal medical records from primary care that can be linked with other health care data. The GPRD is currently collecting information on over 3·6 million active patients (with approximately 13 million patients in total) from around 488 primary care practices across the UK.[11]

Study population

The study population consisted of all patients included in the GPRD who had at least one recorded BMI in the 12–58 kg/m^2 range (inclusive) while ≥18 years of age during the 8-year period between January 1, 2000, and December 31, 2007. The earliest recorded BMI in the 8-year period was defined as the baseline BMI. Incident cases of influenza-associated pneumonia after the date of baseline BMI were identified and included diagnosis of 'influenza with pneumonia' or diagnosis of 'pneumonia' up to 30 days after a diagnosis of 'influenza'. The calendar year of baseline BMI was noted to account for variation in severity of influenza from year to year. The coding system used for diagnostic purposes was the Read clinical classification developed for use with computerized medical information systems.[12] The system is based on five-character alphanumeric codes and was recommended for use in the UK National Health Service in 1990.[13]

BMI was categorized in this study as follows: underweight: <18·5 kg/m^2; acceptable weight (reference): 18·5–24·9 kg/m^2; overweight: 25·0–29·9 kg/m^2; and obese: ≥30·0 kg/m^2. Other baseline characteristics identified were gender, age, type 2 diabetes, hypertension, hypercholesterolemia, hypertriglyceridemia, statin use, antibiotic use, cigarette smoking (current/ex-smoker or non-smoker), and whether vaccinated against influenza or not. Patients with type 2 diabetes were further categorized into eight groups to investigate any interactive effect between BMI and type 2 diabetes relative to an acceptable BMI. The eight subcategorizations were <18·5 kg/m^2 without type 2 diabetes; <18·5 kg/m^2 with type 2 diabetes (the entry date was taken as the later of (i) date of first BMI recording or (ii) date of recording of type 2 diabetes); 18·5–24·9 kg/m^2 without type 2 diabetes (reference); 18·5–24·9 kg/m^2 with type 2 diabetes; 25·0–29·9 kg/m^2 without type 2 diabetes; 25·0–29·9 kg/m^2 with type 2 diabetes; ≥30·0 kg/m^2 without type 2 diabetes; and ≥30·0 kg/m^2 with type 2 diabetes.

Patients were excluded if: they were not permanently registered with a participating general medical practice for a year before and after the date of the first BMI recorded; all BMI results were recorded while they were under 18 years of age; they were pregnant; they had any previous diagnosis of malignant disease (except non-melanoma skin cancer); and they had a history of influenza complications (i.e., 'influenza with pneumonia' or 'pneumonia') 1 year before the first BMI result (n.b. 'influenza' during the year before the first BMI result was allowed).

Data handling

Differences in distributions of baseline characteristics between men and women were assessed by chi-square testing. Observation periods were expressed in person-years

and continued until disenrollment (where patients may have transferred out of or departed from a participating medical practice), the first diagnosis of influenza-associated pneumonia, or the end of the study (whichever came first).

Incidence rates of influenza-associated pneumonia were calculated as the number of new cases per 100 000 person-years for the entire cohort, with stratification according to age, gender, BMI, and BMI with type 2 diabetes; 95% confidence intervals (CIs) were based on a Poisson distribution, with a normal approximation to estimate standard deviations. Unadjusted (crude) and adjusted incidence rate ratios (IRRs) of pneumonia with 95% CIs according to BMI were computed using Poisson regression models (e.g., SAS PROC GENMOD) with a BMI of 18·5–24·9 kg/m^2 as the reference for the full cohort, and stratified by gender. IRRs of pneumonia according to the combination of BMI category and type 2 diabetes status were estimated with BMI equal to 18·5–24·9 kg/m^2 and without type 2 diabetes as reference. Results were then adjusted to account for differences in age, gender, BMI, type 2 diabetes, hypertension, statin use, antibiotic use, smoking status, influenza vaccination, and calendar year at baseline.

Results

The inclusion requirements were satisfied by 1 074 315 patients from the GPRD, of whom 513 385 were men and 560 930 were women. Baseline characteristics of enrolled individuals are shown in Table 1. The highest proportions of patients were in those 40 years of age and older (75·8% of all patients), with the highest proportion in any single age group being 50–59 years of age (21·6% of all patients).

Most patients (73·2% of the total cohort) were within the reference (acceptable) BMI range or were overweight (up to 29·9 kg/m^2). About 24·6% were obese (BMI ≥30), and 2·2% were underweight. More women than men were obese or underweight (Table 1). About 8% of patients had type 2 diabetes.

Of the study cohort, <0·1% were underweight with type 2 diabetes, 1·3% were of acceptable weight with type 2 diabetes, 3·0% were overweight with type 2 diabetes, and 3·7% were obese with type 2 diabetes (Table 1). Proportions of persons who had never smoked and current/ex-smokers were distributed evenly overall, although more women than men had never smoked (Table 1). Cigarette smoking information was incomplete; therefore, proportions of patients do not add up to 100%. The proportion of patients missing smoking information varied by BMI category (15·3% among the underweight, 10·0% among those with acceptable weight, 10·2% among the overweight, and 14·2% among the obese).

Incidence rates of influenza-associated pneumonia (Table 2) showed an increase with age. The highest rates were observed in patients aged 70 and older. The pattern of rates of pneumonia according to BMI category demonstrated an inverse-J relationship with an incidence of 98·29 per 100 000 person-years among the underweight, 37·48 per 100 000 person-years among those of acceptable weight, 32·51 per 100 000 person-years among the overweight, and 32·33 per 100 000 among the obese. There was a gender imbalance in the reference BMI group, where incidence rates were 50·42 (men) and 29·07 (women) per 100 000 person-years (Table 2).

A high incidence rate of pneumonia (64·13 per 100 000 person-years) was noted in patients with type 2 diabetes overall (Table 2). In overweight patients with and without type 2 diabetes, incidence rates of pneumonia were more than two times higher in patients with type 2 diabetes. Rates also appeared almost two times higher in current/ex-smokers than in non-smokers (Table 2). A high rate (78·80 per 100 000 person-years) of pneumonia was also observed in vaccinated patients. Rates were fairly consistent (33·08–38·82 per 100 000 person-years) from 2000 to 2005, but were decreased in 2006 and 2007.

IRRs derived for the various risk categories explored are summarized in Table 3. Unadjusted (crude) and adjusted rate ratios showed a marked increase in the risk of pneumonia in underweight persons (crude IRR = 2·62; 95% CI = 2·10–3·24; adjusted IRR = 2·32; 95% CI = 1·80–2·94), with the highest increased risk being noted in underweight women. Adjustment of IRRs was made to account for age at index date, gender, BMI, type 2 diabetes, hypertension, statin use, antibiotic use, smoking, vaccination status, and calendar year in patients stratified according to (i) BMI category only and (ii) BMI category and presence or absence of type 2 diabetes. Adjusted IRRs indicated an association between diabetes and increased rates of pneumonia among obese women (BMI ≥ 30 kg/m^2; adjusted IRR = 1·47, 95% CI = 1·01–2·06) and confirmed the marked increase in rates of pneumonia among underweight patients, particularly women (adjusted IRR = 2·55, 95% CI = 1·86–3·42).

Discussion

Underweight patients and the elderly in the UK GPRD appeared to have an increased rate of influenza pneumonia and pneumonia following influenza. The finding that the underweight may be at risk for influenza-associated pneumonia may have been overlooked in previous pandemic (H1N1) 2009 influenza studies where obesity was found to be associated with complications. The results of this study are not only different to observations in patients with pandemic influenza, but suggest that the medical community needs to rethink the potential group of patients that should be considered at high risk of pneumonia from seasonal influenza.

Table 1. Baseline characteristics of patients aged ≥18 years [number (%)] identified from the GPRD

Parameter	Categories	Males (*N* = 513 385)	Females (*N* = 560 930)	Total (*N* = 1 074 315)
Age (years)	18–29	60 026 (11·7)	72 657 (13·0)	132 683 (12·4)
	30–39	66 777 (13·1)	61 070 (10·9)	127 847 (11·9)
	40–49	94 993 (18·5)	99 429 (17·7)	194 422 (18·1)
	50–59	112 451 (21·9)	119 523 (21·3)	231 974 (21·6)
	60–69	95 158 (18·5)	94 156 (16·8)	189 314 (17·6)
	≥70	83 980 (16·4)	114 095 (20·3)	198 075 (18·4)
BMI (kg/m^2)	<18·5 (underweight)	7336 (1·4)	16 150 (2·9)	23 486 (2·2)
	18·5–24·9 (acceptable weight)	162 809 (31·7)	231 149 (41·2)	393 958 (36·7)
	25·0–29·9 (overweight)	218 573 (42·6)	174 112 (31·0)	392 685 (36·6)
	≥30·0 (Obese)	124 667 (24·3)	139 519 (24·9)	264 186 (24·6)
Type 2 diabetes	Yes	48 669 (9·5)	37 547 (6·7)	86 216 (8·0)
Hypertension	Yes	3428 (0·7)	3817 (0·7)	7245 (0·7)
Hypercholesterolemia	Yes	78 (0·02)	68 (0·01)	146 (0·01)
Hypertriglyceridemia	Yes	8 (0·00)	3 (0·00)	11 (0·00)
Statin use	Yes	52 822 (10·3)	38 603 (6·9)	91 425 (8·5)
Antibiotic use	Yes	88 462 (17·2)	130 881 (23·3)	219 343 (20·4)
BMI and type 2 diabetes	<18·5 kg/m^2 without type 2 diabetes	7180 (1·4)	15 768 (2·8)	22 948 (2·1)
	<18·5 kg/m^2 with type 2 diabetes	156 (0·03)	382 (0·07)	538 (0·05)
	18·5–24·9 kg/m^2 without type 2 diabetes (reference)	155 602 (30·3)	224 867 (40·1)	380 469 (35·4)
	18·5–24·9 kg/m^2 with type 2 diabetes	7207 (1·4)	6282 (1·1)	13 489 (1·3)
	25·0–29·9 kg/m^2 without type 2 diabetes	198 563 (38·7)	162 163 (28·9)	360 726 (33·6)
	25·0–29·9 kg/m^2 with type 2 diabetes	20 010 (3·9)	11 949 (2·1)	31 959 (3·0)
	≥30·0 kg/m^2 without type 2 diabetes	103 371 (20·1)	120 585 (21·5)	223 956 (20·9)
	≥30·0 kg/m^2 with type 2 diabetes	21 296 (4·2)	18 934 (3·4)	40 230 (3·7)
Smoking status	Never smoked	201 304 (39·2)	284 772 (50·8)	486 076 (45·3)
	Current or ex-smoker	260 269 (50·7)	207 780 (37·0)	468 049 (43·6)
Influenza vaccinations	Yes	37 286 (7·3)	46 533 (8·3)	83 819 (7·8)
Calendar year	2000	79 364 (15·5)	108 698 (19·4)	188 062 (17·5)
	2001	65 079 (12·7)	84 229 (15·0)	149 308 (13·9)
	2002	67 475 (13·1)	78 857 (14·1)	146 332 (13·6)
	2003	69 488 (13·5)	73 000 (13·0)	142 488 (13·3)
	2004	68 354 (13·3)	66 572 (11·9)	134 926 (12·6)
	2005	56 600 (11·0)	54 219 (9·7)	110 819 (10·3)
	2006	69 615 (13·6)	63 697 (11·4)	133 312 (12·4)
	2007	37 410 (7·3)	31 658 (5·6)	69 068 (6·4)

GPRD, General Practice Research Database; BMI, body mass index.

The inverse-J association that was observed between BMI and pneumonia rates is not clear. Indeed, the highest pneumonia rates were in the underweight, and the lowest rates were in the overweight, with overweight status among men being protective. While BMI may have a nonlinear relationship with many conditions, it is possible that overweight patients may have received closer supervision from their general practitioner given their weight status or may have presented with less severe influenza.

Among women (and especially obese women), type 2 diabetes was associated with an increased the rate of pneumonia. This may have been because type 2 diabetes and weight gain are more prevalent in persons aged over 50. Indeed, the largest proportion by age of our study population was accounted for by patients aged over 40. Potential explanations for the observed gender differences include a decrease in immunity because of type 2 diabetes, which may affect women disproportionately as a result of differences in adipose tissue cytokine and hormone levels, and differences in abdominal fat distribution, which may result in a reduced lung volume, an altered ventilation pattern, and a higher risk of aspiration.

In contrast, pandemic (H1N1) 2009 influenza was most common in persons younger than 50 years. We therefore explored this further by examining the subgroup of patients aged 18–49 in the UK GPRD and found that BMI and type

Table 2. Incidence rates of influenza-associated pneumonia according to patient subgroups

Parameter	Categories	Males			Females			Total		
		Cases	Patient-years	Rate per 100 000 person-years (95% CI)	Cases	Patient-years	Rate per 100 000 person-years (95% CI)	Cases	Patient-years	Rate per 100 000 person-years (95% CI)
Age (years)	18–29	19	231 186	8·22 (4·95, 12·83)	18	288 592	6·24 (3·70, 9·86)	37	519 778	7·12 (5·01, 9·81)
	30–39	47	278 733	16·86 (12·39, 22·42)	42	292 218	14·37 (10·36, 19·43)	89	570 951	15·59 (12·52, 19·18)
	40–49	76	403 861	18·82 (14·83, 23·55)	67	477 443	14·03 (10·88, 17·82)	143	881 304	16·23 (13·57, 18·89)
	50–59	140	501 637	27·91 (23·29, 32·53)	103	587 297	17·54 (14·15, 20·92)	243	1 088 934	22·32 (19·51, 25·12)
	60–69	177	429 305	41·23 (35·16, 47·30)	159	448 757	35·43 (29·92, 40·94)	336	878 062	38·27 (34·18, 42·36)
	≥70	447	364 673	122·58 (111·22, 133·93)	416	503 501	82·62 (74·69, 90·56)	863	868 173	99·40 (92·78, 106·03)
BMI (kg/m^2)	<18·5 (Underweight)	29	28 690	101·08 (67·70, 145·17)	65	66 942	97·10 (74·94, 123·76)	94	95 631	98·29 (79·43, 120·29)
	18·5–24·9 (acceptable weight)	345	684 279	50·42 (45·10, 55·74)	306	1 052 558	29·07 (25·82, 32·33)	651	1 736 837	37·48 (34·60, 40·36)
	25·0–29·9 (overweight)	352	953 668	36·91 (33·05, 40·77)	226	820 774	27·53 (23·95, 31·12)	578	1 774 442	32·57 (29·92, 35·23)
	≥30·0 (obese)	180	542 759	33·16 (28·32, 38·01)	208	657 533	31·63 (27·34, 35·93)	388	1 200 292	32·33 (29·11, 35·54)
Type 2 diabetes	Yes	135	206 338	65·43 (54·39, 76·46)	99	158 552	62·44 (50·75, 76·02)	234	364 890	64·13 (55·91, 72·34)
Hypertension	Yes	15	17 850	84·03 (47·03, 138·60)	12	20 861	57·52 (29·72, 100·48)	27	38 711	69·75 (45·96, 101·48)
Hypercholesterolemia	Yes	0	510	0·00 (0·00, 587·07)	0	476	0·00 (0·00, 628·70)	0	987	0·00 (0·00, 303·58)
Hypertriglyceridemia	Yes	0	21	0·00 (0·00, 14293·81)	0	25	0·00 (0·00, 11929·69)	0	46	0·00 (0·00, 6502·59)
Statin use	Yes	146	224 611	65·00 (54·46, 75·54)	92	164 762	55·84 (45·01, 68·48)	238	389 373	61·12 (53·36, 68·89)
Antibiotic use	Yes	305	386 065	79·00 (70·14, 87·87)	288	608 278	47·35 (41·88, 52·81)	593	994 343	59·64 (54·84, 64·44)
BMI and type 2 diabetes	<18·5 kg/m^2 without type 2 diabetes	28	28 139	99·50 (66·12, 143·81)	61	65 710	92·83 (71·01, 119·25)	89	93 849	94·83 (76·16, 116·70)
	<18·5 kg/m^2 with type 2 diabetes	1	550	181·74 (4·60, 1012·59)	4	1232	324·73 (88·48, 831·43)	5	1782	280·58 (91·10, 654·77)
	18·5–24·9 kg/m^2 without type 2 diabetes	320	653 041	49·00 (43·63, 54·37)	282	1 026 081	27·48 (24·28, 30·69)	602	1 679 122	35·85 (32·99, 38·72)
	18·5–24·9 kg/m^2 with type 2 diabetes	25	31 238	80·03 (51·79, 118·14)	24	26 477	90·64 (58·08, 134·87)	49	57 715	84·90 (62·81, 112·24)
	25·0–29·9 kg/m^2 without type 2 diabetes	291	866 099	33·60 (29·74, 37·46)	197	768 959	25·62 (22·04, 29·20)	488	1 635 058	29·85 (27·20, 32·49)
	25·0–29·9 kg/m^2 with type 2 diabetes	61	87 569	69·66 (53·28, 89·48)	29	51 815	55·97 (37·48, 80·38)	90	139 384	64·57 (51·92, 79·37)
	≥30·0 kg/m^2 without type 2 diabetes	132	455 778	28·96 (24·02, 33·90)	166	578 506	28·69 (24·33, 33·06)	298	1 034 283	28·81 (25·54, 32·08)
	≥30·0 kg/m^2 with type 2 diabetes	48	86 981	55·18 (40·69, 73·17)	42	79 028	53·15 (38·30, 71·84)	90	166 008	54·21 (43·59, 66·64)
Smoking status	Never smoked	218	857 627	25·42 (22·05, 28·79)	303	1 302 484	23·26 (20·64, 25·88)	521	2 160 111	24·12 (22·05, 26·19)
	Current or ex-smoker	587	1 095 669	53·57 (49·24, 57·91)	376	936 471	40·15 (36·09, 44·21)	963	2 032 140	47·39 (44·40, 50·38)
Influenza vaccinations	Yes	173	171 283	101·00 (85·96, 116·05)	136	220 839	61·58 (51·24, 71·93)	309	392 121	78·80 (70·02, 87·59)

Table 2. Continued

Parameter	Categories	Males			Females			Total		
		Cases	Patient-years	Rate per 100 000 person-years (95% CI)	Cases	Patient-years	Rate per 100 000 person-years (95% CI)	Cases	Patient-years	Rate per 100 000 person-years (95% CI)
Calendar year	2000	278	524 811	52·97 (46·75, 59·20)	211	734 722	28·72 (24·84, 32·59)	489	1 259 532	38·82 (35·38, 42·26)
	2001	146	391 534	37·29 (31·24, 43·34)	154	515 371	29·88 (25·16, 34·60)	300	906 905	33·08 (29·34, 36·82)
	2002	159	359·050	44·28 (37·40, 51·17)	136	426 482	31·89 (26·53, 37·25)	295	785 532	37·55 (33·27, 41·84)
	2003	127	317 846	39·96 (33·01, 46·90)	100	336 836	29·69 (23·87, 35·51)	227	654 682	34·67 (30·16, 39·18)
	2004	94	258 319	36·39 (29·41, 44·53)	94	252 959	37·16 (30·03, 45·47)	188	511 278	36·77 (31·52, 42·03)
	2005	59	165 835	35·58 (27·08, 45·89)	64	158 943	40·27 (31·01, 51·42)	123	324 778	37·87 (31·18, 44·56)
	2006	33	142 360	23·18 (15·96, 32·55)	30	130 602	22·97 (15·50, 32·79)	63	272 962	23·08 (17·74, 29·53)
	2007	10	49 640	20·15 (9·66, 37·05)	16	41 894	38·19 (21·83, 62·02)	26	91 533	28·40 (18·56, 41·62)
Overall		906	2 209 395	41·01 (38·34, 43·68)	805	2 597 807	30·99 (28·85, 33·13)	1711	4 807 202	35·59 (33·91, 37·28)

BMI, body mass index; CI, confidence interval.

2 diabetes were not independent risk factors for pneumonia. Moreover, no interaction between BMI category and type 2 diabetes was detected in persons in this age group.

Other factors that increased pneumonia rates in this population were cigarette smoking and receiving a vaccination, although this may not be surprising. The general and respiratory risks of smoking are well known, and vaccination programs are designed to target groups of patients at high risk, which implies that patients at higher risk were more likely to have been vaccinated. These observations may give rise to speculation over the protective effect of vaccination against pneumonia in high-risk individuals; however, this would require further investigation as the present study was not designed to test such a hypothesis.

Recent work on the risk of complications of influenza has indicated that there is a risk of increased morbidity in cases of pandemic (H1N1) 2009 influenza where obesity is present, although this remains unconfirmed and further research is required. Kumar *et al.*,[7] who studied 168 critically ill patients in 38 adult and pediatric ICUs in Canada between April 16, 2009, and August 12, 2009, for the Canadian Critical Care Trials Group H1N1 Collaborative, have pointed out that obesity is a risk factor for increased morbidity but not consistently for mortality in critically ill patients generally. The association of obesity with severe disease may be a novel finding associated with the 2009 pandemic. There was no association with mortality in cohorts of critically ill patients in Canada or Mexico.[5,7] The Michigan group,[4] who pointed out the need for clinicians to be aware of the potential for severe complications in severely obese patients with pandemic influenza, studied a very small number (10) of intensive care cases only, and the findings summarized in the introduction to the present article must therefore be viewed with this in mind.

These interesting and novel findings highlight the need for further discussion of issues affecting risks and outcomes in patients with various types of influenza. Data are available from various studies that have attempted to shed light on potentially relevant metabolic and immunologic factors. A number of experimental models point to an effect of BMI on immune function, for example, but nevertheless fail to explain the present findings. Smith *et al.*[14] found that in mice obesity inhibited the ability of the immune system to respond to influenza infection. This was characterized by minimal induction of interferons, delayed expression of pro-inflammatory cytokines and chemokines, and impaired natural killer cell cytotoxicity.

Abdominal obesity is known to play a part in the development of insulin resistance, type 2 diabetes, and atherosclerosis, but possible associations between increased BMI and immune changes when infective agents are present are unclear. Bouwman *et al.*[15] showed that infection of adipocytes *in vitro* with a range of infective agents (which

Table 3. Incidence rate ratios (IRRs) of influenza-associated pneumonia by BMI, metabolic disease status, use of select medications, cigarette smoking status, influenza vaccination, and calendar year

Category	Parameter	Categories	IRRs (95% CIs)		
			Males	Females	Total
Crude IRRs	BMI (kg/m^2)	<18·5 (Underweight)	2·00 (1·34, 2·87)	3·34 (2·53, 4·33)	2·62 (2·10, 3·24)
		18·5–24·9 (acceptable weight)	Reference		
		25·0–29·9 (Overweight)	0·73 (0·63, 0·85)	0·95 (0·80, 1·12)	0·87 (0·78, 0·97)
		≥30·0 (Obese)	0·66 (0·55, 0·79)	1·09 (0·91, 1·30)	0·86 (0·76, 0·98)
	Type 2 diabetes	No	Reference		
		Yes	1·70 (1·41, 2·03)	2·16 (1·74, 2·65)	1·93 (1·68, 2·21)
	Hypertension	No	Reference		
		Yes	2·07 (1·19, 3·31)	1·87 (1·00, 3·15)	1·98 (1·32, 2·83)
	Statin use	No	Reference		
		Yes	1·70 (1·42, 2·02)	1·91 (1·52, 2·35)	1·83 (1·59, 2·10)
	Antibiotic use	No	Reference		
		Yes	2·40 (2·09, 2·75)	1·82 (1·58, 2·10)	2·03 (1·84, 2·25)
	BMI and type 2 diabetes	<18·5 kg/m^2 without type 2 diabetes	2·03 (1·35, 2·93)	3·38 (2·54, 4·42)	2·65 (2·10, 3·29)
		<18·5 kg/m^2 with type 2 diabetes	3·71 (0·21, 16·42)	11·82 (3·65, 27·71)	7·83 (2·80, 16·90)
		18·5–24·9 kg/m^2 without type 2 diabetes	Reference		
		18·5–24·9 kg/m^2 with type 2 diabetes	1·63 (1·06, 2·40)	3·30 (2·12, 4·89)	2·37 (1·75, 3·13)
		25·0–29·9 kg/m^2 without type 2 diabetes	0·69 (0·58, 0·80)	0·93 (0·78, 1·12)	0·83 (0·74, 0·94)
		25·0–29·9 kg/m^2 with type 2 diabetes	1·42 (1·07, 1·85)	2·04 (1·36, 2·93)	1·80 (1·43, 2·23)
		≥30·0 kg/m^2 without type 2 diabetes	0·59 (0·48, 0·72)	1·04 (0·86, 1·26)	0·80 (0·70, 0·92)
		≥30·0 kg/m^2 with type 2 diabetes	1·13 (0·82, 1·51)	1·93 (1·38, 2·64)	1·51 (1·20, 1·88)
	Smoking status	Never smoked	Reference		
		Current or ex-smoker	2·11 (1·81, 2·47)	1·73 (1·48, 2·01)	1·96 (1·77, 2·19)
	Influenza vaccinations	No	Reference		
		Yes	2·81 (2·37, 3·31)	2·19 (1·81, 2·62)	2·48 (2·19, 2·80)
	Calendar year	2000	2·29 (1·62, 3·34)	1·25 (0·87, 1·87)	1·68 (1·30, 2·21)
		2001	1·61 (1·12, 2·39)	1·30 (0·89, 1·96)	1·43 (1·10, 1·90)
		2002	1·91 (1·33, 2·83)	1·39 (0·95, 2·10)	1·63 (1·25, 2·15)
		2003	1·72 (1·19, 2·57)	1·29 (0·87, 1·98)	1·50 (1·14, 2·00)
		2004	1·57 (1·07, 2·37)	1·62 (1·09, 2·48)	1·59 (1·21, 2·13)
		2005	1·53 (1·01, 2·37)	1·75 (1·15, 2·74)	1·64 (1·22, 2·24)
		2006	Reference		
		2007	0·87 (0·41, 1·70)	1·66 (0·89, 3·01)	1·23 (0·77, 1·92)
Adjusted IRRs*	BMI (kg/m^2)	<18·5 (Underweight)	2·06 (1·31, 3·08)	2·55 (1·86, 3·42)	2·32 (1·80, 2·94)
		18·5–24·9 (acceptable weight)	Reference		
		25·0–29·9 (overweight)	0·69 (0·59, 0·81)	0·87 (0·72, 1·04)	0·77 (0·68, 0·86)
		≥30·0 (obese)	0·76 (0·63, 0·92)	1·12 (0·92, 1·35)	0·92 (0·80, 1·05)
	Type 2 diabetes	No	Reference		
		Yes	1·03 (0·84, 1·26)	1·37 (1·08, 1·72)	1·16 (0·99, 1·35)
	Hypertension	No	Reference		
		Yes	1·59 (0·89, 2·59)	1·27 (0·64, 2·25)	1·43 (0·93, 2·10)
	Statin use	No	Reference		
		Yes	1·04 (0·86, 1·26)	0·98 (0·77, 1·24)	1·02 (0·88, 1·18)
	Antibiotic use	No	Reference		
		Yes	1·97 (1·70, 2·28)	1·65 (1·41, 1·93)	1·81 (1·62, 2·01)
	BMI and type 2 diabetes	<18·5 kg/m^2 without type 2 diabetes	2·05 (1·29, 3·08)	2·64 (1·91, 3·56)	2·34 (1·80, 2·98)
		<18·5 kg/m^2 with type 2 diabetes	2·02 (0·11, 8·95)	2·66 (0·44, 8·31)	2·31 (0·57, 6·03)
		18·5–24·9 kg/m^2 without type 2 diabetes	Reference		
		18·5–24·9 kg/m^2 with type 2 diabetes	0·89 (0·56, 1·33)	1·54 (0·94, 2·38)	1·14 (0·82, 1·54)
		25·0–29·9 kg/m^2 without type 2 diabetes	0·67 (0·57, 0·80)	0·86 (0·71, 1·05)	0·76 (0·67, 0·86)
		25·0–29·9 kg/m^2 with type 2 diabetes	0·76 (0·55, 1·03)	1·16 (0·75, 1·73)	0·91 (0·71, 1·16)
		≥30·0 kg/m^2 without type 2 diabetes	0·71 (0·57, 0·88)	1·09 (0·88, 1·34)	0·88 (0·76, 1·02)
		≥30·0 kg/m^2 with type 2 diabetes	0·90 (0·64, 1·23)	1·47 (1·01, 2·06)	1·12 (0·88, 1·42)

BMI, body mass index; CI, confidence interval.
*Adjusted for age at index date, gender, BMI, type 2 diabetes, hypertension, statin use, antibiotic use, cigarette smoking status, influenza vaccination status, and year of index date.

included influenza A, *Chlamydia pneumoniae*, cytomegalovirus, adenoviruses, and respiratory syncitial virus) produced pro-inflammatory changes, although specific effects of influenza A on interleukin, plasminogen activator inhibitor-1, adiponectin, and tumor necrosis factor-α production were not shown. On the other hand, obesity has been shown to interfere with cellular responses during influenza infection leading to T-cell alterations, according to studies of dendritic cell function in mice with diet-induced obesity.[16]

Beyond the laboratory, Chubak *et al.*[17] showed reduced incidence of the common cold after 1 year of moderate intensity exercise among 115 post-menopausal women who had previously been overweight or obese. While these findings are of public health relevance and add a new dimension to the benefits of moderate exercise, their relevance to patients who might contract influenza remain unknown.

Low BMI has been associated (albeit inconclusively) with respiratory disease elsewhere. Cao *et al.*[18] identified a high prevalence of underweight individuals in their cross-sectional study of 186 patients with moderate to severe chronic obstructive pulmonary disease and one or more admissions for acute exacerbations to two general hospitals. However, no link between low body weight and frequent readmission was demonstrated by either univariate or multivariate analyses.

Associations between nutritional status and immune function have also been shown. Protein-energy malnutrition is associated with infectious disease, including influenza.[19] Older, energy-restricted mice show increased rates of mortality in response to primary influenza infection, possibly because of a link between low body weight and failure to meet energy demands associated with the immune response to primary viral infection.[19] Infections have adverse effects on nutritional status, but conversely almost any nutrient deficiency can potentially impair resistance to infection. A comprehensive review of the literature on this subject[20] highlighted the close relationship between nutritional status and infection and underlined the public health importance of iron deficiency and protein-energy malnutrition in this respect. Trace element deficiencies are also associated with defective immune function: zinc, for example, is essential for immune development and maintenance, and more than 100 metalloenzymes are zinc dependent. Other elements of potential interest in this respect include copper, magnesium, and selenium.[20]

Low BMI (<18 kg/m^2) is known to be associated with compromised immunity in humans.[19] A history of weight loss worsens clinical prognosis in elderly hospitalized persons, and studies suggest that low or even normal body weight may be predictive of increased mortality in the elderly, while increased weight may have a protective effect.[19] Influenza infection itself results in anorexia mediated at least partly by chemokine and cytokine responses, and additional weight loss impedes recovery.[19] A history of weight loss in elderly persons was associated with an increased incidence of complications of hospitalization in 110 persons admitted to the geriatric rehabilitation unit of a Veterans' Administration hospital in the United States.[21] The risk of developing at least one complication was found by multivariate analysis to be associated with functional status and serum albumin level on admission and the amount of weight lost in the year preceding admission (in addition to the presence or absence of pulmonary or renal disease).

It is not clear whether the results of this study sample are generalizable to the entire patient cohort of the United Kingdom. Exclusion criteria were not especially stringent; patients not permanently registered with a participating general medical practice, patients who were pregnant or who had a history of malignant disease or influenza complications in the year prior to the first BMI were excluded from the study. In 1997, data on height and weight were available for over 70% of the UK primary care population, presumably many of whom were not overweight or obese. This relatively large percentage is noteworthy in that it was primarily before increased awareness of the obesity epidemic in the UK. Since that time, BMI measurements have become more standard in the GPRD. Because there is relatively little published data on obesity and/or diabetes and the incidence of influenza or influenza complications, it seems unlikely that a general practitioner would specifically collect BMI data to monitor for acute sequelae associated with influenza. Thus, any selection bias may be non-differential and minimal. Moreover, the statistical models accounted for baseline differences among patients in different BMI categories. Similarly, any misclassification of influenza-associated pneumonia would be no more likely to occur in one BMI category versus another. These UK GPRD patients were not derived from a hospitalized cohort, and therefore, overall rates of pneumonia may be lower compared with a pandemic (H1N1) 2009 cohort. Still, the objective of the present study was to examine the natural history and select risk factors for seasonal influenza.

The finding that being underweight was associated with a higher incidence of pneumonia, while rates were lower in the overweight should be interpreted with caution but nevertheless merits discussion because of its public health implications.[22]

Conclusions

Recent research has shown a possible link between high BMI/obesity and increased morbidity rates in patients with the pandemic influenza A (H1N1) strain that emerged in

April 2009. These observations are supported to some extent by animal, and other data showing immunologic and other effects of obesity. The results of our retrospective cohort study of UK patients, however, suggest that underweight persons, particularly women, have an increased rate of influenza-associated pneumonia relative to persons of normal weight. The reasons for this and for the apparent inconsistency with observations in patients with pandemic influenza are unclear, although we also noted an apparent association between diabetes in women (particularly the obese) and increased risk of influenza-associated pneumonia. Associations between weight loss or malnutrition and infectious disease have been demonstrated in the literature, with infection having been shown to affect nutritional status and *vice versa*. Notably in this respect, cachexia is unlikely to have been a factor in the present cohort as patients with malignant disease were not included. Our findings in individuals with seasonal influenza are therefore consistent with observations of weight loss linked to infectious disease, but the associations between BMI status and outcomes in influenza infection remain unclear and require further study.

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Conflict of interest

S. Toovey is a former employee and paid consultant to F. Hoffmann-La Roche, manufacturer and distributor of oseltamivir; he has received fees for speaking and attending symposia. W. Blumentals and M. Peng are employed by Hoffmann-La Roche, Inc., and have conducted a number of safety and effectiveness studies for oseltamivir. The results presented in this work would not impact company business in any way.

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