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BRIEF REPORT

Obesity Increases the Duration of Influenza A Virus Shedding in Adults

Hannah E. Maier,[1] Roger Lopez,[3,5] Nery Sanchez,[5] Sophia Ng,[1] Lionel Gresh,[5] Sergio Ojeda,[5] Raquel Burger-Calderon,[2,5] Guillermina Kuan,[4,5] Eva Harris,[2] Angel Balmaseda,[3,5] and Aubree Gordon[1]

[1]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor; [2]Division of Infectious Diseases and Vaccinology, School of Public Health, University of California, Berkeley; and [3]Centro Nacional de Diagnóstico y Referencia and [4]Centro de Salud Sócrates Flores Vivas, Ministry of Health, and [5]Sustainable Sciences Institute, Managua, Nicaragua

(See the Editorial Commentary Schultz-Cherry, on pages 1354–5.)

Epidemiologic studies indicate that obesity increases the risk of severe complications and death from influenza virus infections, especially in elderly individuals. This work investigates the effect of obesity on the duration of viral shedding within household transmission studies in Managua, Nicaragua, over 3 seasons (2015–2017). Symptomatic obese adults were shown to shed influenza A virus 42% longer than nonobese adults (adjusted event time ratio [ETR], 1.42; 95% confidence interval [CI], 1.06–1.89); no association was observed with influenza B virus shedding duration. Even among paucisymptomatic and asymptomatic adults, obesity increased the influenza A shedding duration by 104% (adjusted ETR, 2.04; 95% CI, 1.35–3.09). These findings suggest that obesity may play an important role in influenza transmission.

Keywords. Influenza virus; obesity; viral shedding; paucisymptomatic; asymptomatic; transmission; household; epidemiology; public health.

Epidemiologic studies indicate that obesity increases the risk of severe complications and death from influenza virus infections, especially in elderly individuals [1, 2]. The global prevalence of obesity has increased dramatically over the last few decades. The regional burden varies widely—in 2014, the prevalence of adult obesity in the United States was 35.5%, compared with 17.4% in Nicaragua and 4.4% in other low-income economies—but in every region, adult obesity is increasing, and the pace of increase is accelerating [3].

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Correspondence: A. Gordon, PhD, 5622 SPH I, School of Public Health, 1415 Washington Heights, Ann Arbor, MI 48109-2029 (gordonal@umich.edu)

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Both the duration and quantity of viral shedding influence influenza transmission [4, 5]. Children are known to be important for influenza transmission, and young age has been associated with longer duration of shedding [6]. Shedding has also been shown in paucisymptomatic and asymptomatic influenza cases, highlighting the transmission potential of less severe cases [7].

Obesity leads to altered immune function and chronic inflammation, which increases with age, in addition to mechanical difficulties in breathing and increased oxygen requirements [8–10]; these are plausible mechanisms by which obesity could alter influenza risk, severity, and transmission potential. We hypothesize that this immune dysfunction could lead to a longer duration of influenza virus shedding, possibly increasing the transmission potential of infected individuals. While obesity is associated with severe influenza outcomes [1, 2], the effect of obesity on less severe influenza infections and transmission dynamics has not been as well studied. Here, we use household influenza transmission studies to examine the association between obesity and influenza virus shedding duration.

METHODS

Study Population and Procedures

This work uses data from 2 studies of households in the catchment area of the Health Center Sócrates Flores Vivas (HCSFV) in District II of Managua, the capital of Nicaragua. Three influenza seasons are included: late 2015, 2016/2017, and mid/late 2017. The Household Influenza Transmission Study (HITS) has a case-ascertained design, in which cases were identified from the HCSFV study clinic and their households enrolled; it provided data for the first 2 seasons. The Household Influenza Cohort Study (HICS) has the same design features as the HITS; it is nested within a prospective cohort study, in which enrollment occurs before the introduction of influenza to the households. The HICS started in 2017 and provided data from the 2017 influenza season. Height and weight measurements were collected at enrollment. Each measurement was taken twice; if there was a difference of >5% between the 2 measurements, a third was taken. Measurements were averaged.

For both studies, participating household members were intensively monitored for 10–13 days once a symptomatic influenza case was identified in the household. A full description of the inclusion criteria has previously been published [6]. Daily symptom diaries were recorded for all participants and up to 5 combined nasal/oropharyngeal swab specimens, and temperatures were measured for each household contact during follow-up, regardless of symptoms. As with our other studies, if a participant visited the HCSFV study clinic while enrolled,

data from the visit were collected and were available for study use [11]. As described previously, all respiratory swab samples are tested by reverse transcription polymerase chain reaction (RT-PCR) analysis following validated Centers for Disease Control and Prevention protocols for influenza A and B virus detection [6]. Subtype and lineage are obtained for all influenza A and B virus–positive samples, respectively, through additional RT-PCR assays.

Ethics Statement

These studies were approved by the institutional review boards at the Nicaraguan Ministry of Health, the University of Michigan, and the University of California, Berkeley. Informed consent or parental permission for minors was obtained from all participants. Assent was obtained for children aged ≥6 years.

Weight Status

Body mass index (BMI) *z* scores were calculated for children <18 years old, based on the World Health Organization child growth standard for children aged <5 years and reference for children aged 5–17 years [12, 13]. BMI was calculated for adults as the weight in kilograms divided by the height in meters squared. Obesity was defined as a BMI of ≥30 in adults and as a BMI *z* score of >3 or >2 for children aged <5 or 5–17 years, respectively. Underweight was defined as a BMI of <18.5 in adults and as a BMI *z* score of ≤2 in children. The nonobese reference group was defined as those who were not underweight or obese.

Shedding Duration

Shedding duration was defined as the time from illness onset to viral shedding cessation, as described previously [6]. Symptom data were obtained from daily symptom diaries and clinic visits, and illness was defined as acute respiratory illness (ARI2) with at least 2 of the following symptoms: measured fever (temperature >37.8°C) or reported fever, sore throat, cough, or runny nose on any day. Illness onset was defined as the earlier of the day that symptoms first appeared or that RT-PCR results were positive; if there were gaps >2 days without symptoms, illness onset was defined as the first day of the symptomatic period closest to the RT-PCR–positive event. Shedding cessation was defined either as occurring in the interval between the last positive RT-PCR result and subsequent negative RT-PCR result (interval censoring) or as right censored if the participant's last sample was RT-PCR positive. To minimize left censoring, we restricted this analysis to secondary cases.

In sensitivity analyses, illness was also defined as RT-PCR positivity (regardless of symptoms) and as influenza-like illness (ILI; defined as measured or reported fever with cough or sore throat).

Statistical Methods

Parametric accelerated failure time (AFT) models with Weibull distributions, which can handle censored data, adjusted for age and sex, were used to calculate event time ratios (ETRs) to compare shedding duration in obese versus nonobese participants [4, 5]. Statistical analyses were conducted in R, version 3.4.3 (available at: https://www.R-project.org/), using the package "Survival" (https://CRAN.R-project.org/package=survival), to run the AFT models and to predict mean shedding duration accounting for age and sex; "SurvRegCensCov" (https://CRAN.R-project.org/package=SurvRegCensCov), to convert the model output to ETRs; and "ggplot2" (http://ggplot2.org), for plotting.

RESULTS

Study Population

In total, 1783 people in 320 households participated in intensive monitoring periods. The HITS contributed 800 participants from the first 2 seasons, and the HICS contributed 983 participants in 2017 who were enrolled in intensive monitoring periods. These individuals provided 7066 swab samples for testing, with a mean number of 4.0 swabs/participant. Symptoms were reported for 15 905 days, with a median symptom diary duration of 10 days. There were 340, 631, and 812 participants in age groups 0–4, 5–17, and 18–92 years, respectively. Sex ratios were approximately equal in children but not equally distributed in adults, among whom 74% were women. The obesity prevalence varied significantly by age, with 2%, 9%, and 42% aged 0–4, 5–17, and 18–92 years, respectively.

Secondary cases aged 5–92 years made up 287 of 694 RT-PCR–positive influenza cases (41.3%); of these, 4 (1.4%) were missing height and weight data, and 9 (3.1%) were underweight and were excluded from analysis, leaving 276 secondary cases. Prevalence of obesity was similar among these secondary cases as compared to the overall study population that participated in intensive monitoring periods (Supplementary Table 1).

Of the 276 secondary cases included in the analysis, 19.9% were infected with 2009 pandemic influenza A(H1N1) virus, 38% were infected with influenza A(H3N2) virus, and 42% were infected with influenza B virus. Supplementary Figure 1 shows the epidemic curves by influenza virus type for each season (numbers are provided in Supplementary Table 2).

Shedding Duration

Children aged 0–4 years shed influenza virus 40% longer (crude ETR, 1.40; 95% confidence interval [CI], 1.22–1.60) and children aged 5–17 years shed influenza virus 30% longer (crude ETR, 1.30; 95% CI, 1.15–1.48) than adults aged 18–92 years. These trends were similar for both influenza A and B viruses (Supplementary Table 3). However, influenza B virus shedding was longer and displayed larger variance than influenza A virus shedding for all ages. Mean predicted influenza virus shedding duration was 7.7 days, 7.2 days, and 5.5 days for ages 0–4, 5–17, and 18–92 years, respectively. Mean predicted shedding duration among individuals aged 0–4, 5–17, and 18–92 years was

7.0, 6.4, and 5.1 days, respectively, for influenza A virus and 9.3, 8.8, and 6.4 days, respectively, for influenza B virus.

Obesity and Shedding Duration

Symptomatic obese adults shed influenza A virus 42% longer (adjusted ETR, 1.42; 95% CI, 1.06–1.89) than nonobese adults, with predicted mean shedding times of 5.23 days versus 3.68 days. They also shed influenza A(H1N1) virus 43% longer than nonobese adults (adjusted ETR, 1.43; 95% CI, 1.02–2.02). No association was observed between obesity and shedding duration for influenza B virus (Table 1 and Figure 1). Obesity was not associated with shedding duration in children aged 5–17 years (Supplementary Table 4). There were not enough obese secondary cases aged <5 years old to include in this analysis.

Varying the shedding definition in sensitivity analyses did not substantially influence our findings, although for influenza A(H3N2) virus, the association increased when using the ILI definition, and all associations increased when using the definition based on RT-PCR positivity regardless of symptoms (Supplementary Table 5).

Obese individuals with influenza tended to have more symptomatic/severe illness, and fewer obese individuals had asymptomatic influenza, although the differences were not significant (Supplementary Table 6). To examine whether the association of obesity and increased shedding duration existed among less symptomatic adults, the same analyses were performed among cases who had ≤1 symptom, not including fever. Of the 147 adult influenza cases, 40.8% had ILI, 69.4% had ARI2, 11.6% were paucisymptomatic (not including fever), and 17.7% were asymptomatic; among nonobese cases, 16.5% were paucisymptomatic, and 18.7% were asymptomatic, compared with 3.6% and 16.1% of obese cases, respectively. Among cases with ≤1 symptom not including fever, obese adults shed influenza A virus 104% longer than nonobese adults (adjusted ETR, 2.04; 95% CI, 1.35–3.09).

Table 1. Accelerated Failure Time Models of Obesity and Shedding Duration Among Adult Secondary Influenza Cases Aged 18-92 Years, by Influenza Virus Type and Strain

Variable	Crude ETR (95% CI)	Adjusted[a] ETR (95% CI)	Predicted Shedding Duration, Mean Days (IQR)
Symptomatic illness (ARI2)			
All influenza viruses (n = 102)			
Nonobese	Reference	Reference	4.67 (2.82–6.93)
Obese	1.14 (.86–1.50)	1.14 (.87–1.50)	5.32 (3.22–7.90)
By influenza virus type			
A (n = 62)			
Nonobese	Reference	Reference	3.68 (2.41–5.13)
Obese	1.42 (1.05–1.92)	1.42 (1.06–1.89)	5.23 (3.42–7.30)
B (n = 40)			
Nonobese	Reference	Reference	6.55 (3.79–10.07)
Obese	0.80 (.48–1.35)	0.82 (.49–1.39)	5.40 (3.13–8.30)
By influenza A virus subtype			
H1N1 (n = 23)			
Nonobese	Reference	Reference	3.56 (2.65–4.49)
Obese	1.75 (1.12–2.71)	1.43 (1.02–2.02)	5.10 (3.80–6.44)
H3N2 (n = 39)			
Nonobese	Reference	Reference	3.77 (2.40–5.41)
Obese	1.22 (.81–1.84)	1.23 (.91–1.98)	5.05 (3.21–7.24)
Paucisymptomatic[b]/asymptomatic illness			
All influenza viruses (n = 43)			
Nonobese	Reference	Reference	1.97 (1.31–2.72)
Obese	1.55 (.91–2.65)	1.43 (.85–2.41)	2.81 (1.87–3.89)
By influenza virus type			
A (n = 25)			
Nonobese	Reference	Reference	1.57 (1.26–1.87)
Obese	2.35 (1.62–3.42)	2.04 (1.35–3.09)	3.21 (2.57–3.82)
B (n = 18)			
Nonobese	Reference	Reference	2.37 (1.49–3.41)
Obese	1.35 (.39–4.61)	1.07 (.30–3.81)	2.54 (1.60–3.65)

Abbreviations: ARI2, acute respiratory illness (see Methods for definition); CI, confidence interval; ETR, event time ratio; IQR, interquartile range.

[a]Models adjusted for age and sex.

[b]Paucisymptomatic cases have 1 symptom, not including fever

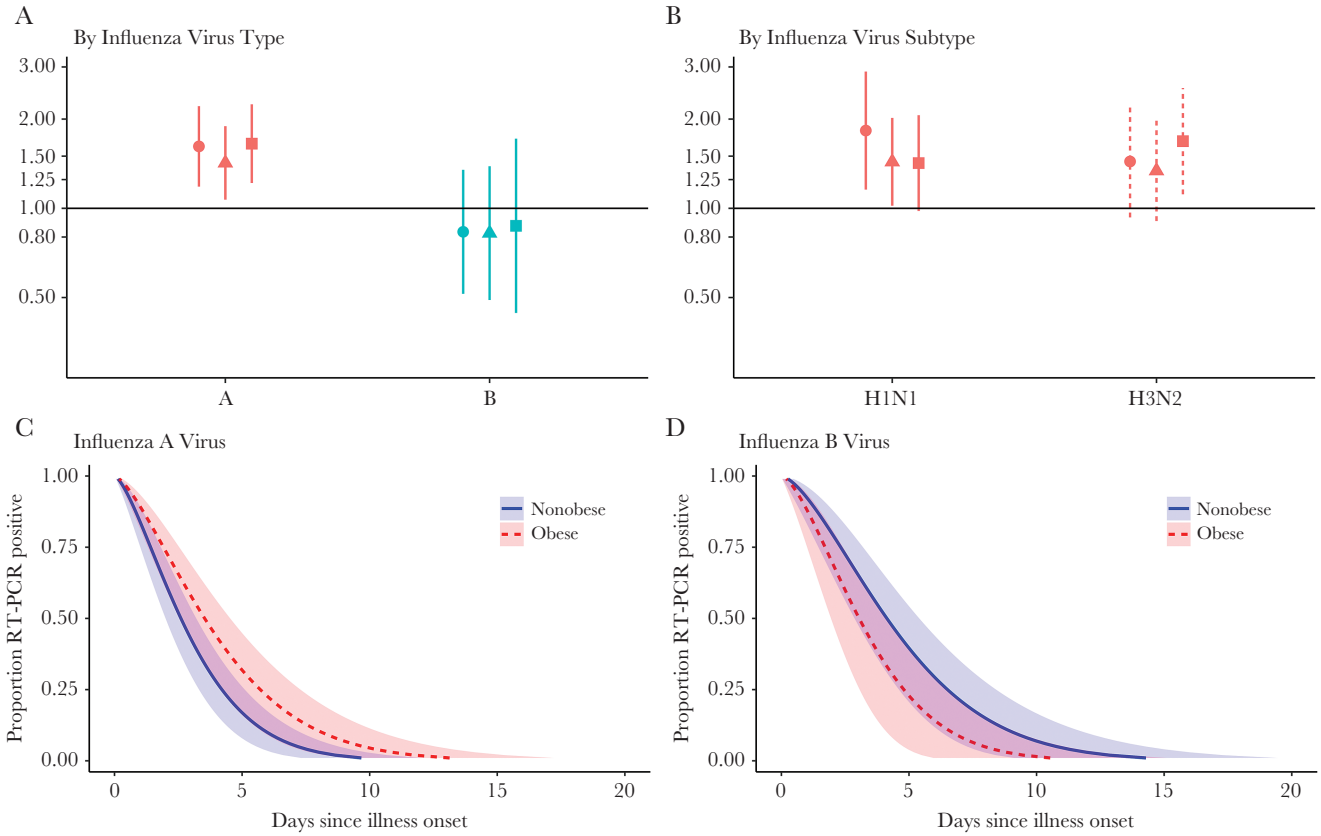

Figure 1. Association of obesity and influenza virus shedding in adults. *A* and *B*, Event time ratios adjusted for age and sex, by influenza virus type (*A*) and subtype (*B*), among obese relative to nonobese adults. Red indicates ratios for influenza A virus, and blue indicates ratios for influenza B virus. Shapes refer to illness onset definition, with circles indicating reverse transcription (RT-PCR)–based illness; triangles, acute respiratory illness (see Methods for definition); and squares, influenza-like illness. *C* and *D*, Predicted shedding duration of influenza A virus (*C*) and influenza B virus (*D*), using the RT-PCR–based illness definition.

DISCUSSION

While previous studies identified obesity as a risk factor for severe influenza outcomes [1, 2], we showed that obesity also affects less severe outcomes by significantly increasing the duration of influenza A virus shedding in adults. Further, we found that, even in asymptomatic or mildly ill individuals, obese adults shed influenza A virus for a longer duration than nonobese adults. This has important implications for influenza transmission.

No association was found with obesity and duration of influenza B virus shedding. It is unclear why this association is specific to influenza A virus, but it is consistent with previous findings of obesity and severe influenza outcomes primarily for influenza A(H1N1) virus [1, 2]. Human challenge studies also found more variability in influenza B virus shedding, compared with influenza A(H1N1) virus shedding [14]. Obesity was not associated with shedding duration in children 5–17 years old. This is in agreement with the hypothesis that obesity increases the shedding duration through chronic inflammation. The study was underpowered to assess this association in children aged <5 years.

In addition to studies of obesity and influenza severity, a recent study that sampled exhaled breath from college students with influenza for virus found an association between obesity and how much virus is shed. The authors noted that most participants had nasal shedding and that obesity was associated with increased aerosol-based shedding; however, they did not assess whether obese individuals shed virus for a longer duration than nonobese individuals [15].

Here we focus on shedding duration, but virus quantity is also important; both are assumed to be positively associated with transmission, although the relationship was not found to be directly proportional within households and needs more investigation [5]. Owing to differences in contact patterns and types, transmission occurs earlier within households than in the wider community, which may reduce the impact of shedding duration on transmission in the household setting [4, 16]. Further analyses are underway to examine the effect of obesity on influenza transmission in Nicaraguan households.

This study had several limitations. Nose and throat samples were only collected every 2–3 days (interval censoring), and cases for whom final samples were RT-PCR positive were right

censored, preventing observation of the precise shedding cessation time. Shedding was measured by RT-PCR, which only measures the presence of viral RNA but does not indicate whether the virus is infectious. In addition, quantitative data could have provided additional evidence on viral shedding, however, quantification standards were not available at the time of testing.

This work has identified obesity as an important predictor of influenza A virus shedding duration in adults. Obesity may play an important role in influenza transmission, especially as the prevalence of obesity rises, and may be an important target for intervention and prevention strategies. Further, these results add to existing evidence linking obesity to infectious diseases, making it now even more important to work toward controlling and preventing the obesity epidemic.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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