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Herpesvirus reactivation and socioeconomic position: a community-based study

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Abstract

Background—Elevated antibodies to latent herpesviruses have been demonstrated to be a reliable marker of diminished cellular immunity and recently have been associated with low socioeconomic position (SEP) in older adults. Extending these observations in a community-based study over a wide age range would provide an important new direction for investigating mechanisms underlying poor health outcomes in individuals with low SEP.

Methods—Anti-herpes simplex virus (HSV)-1 and anti-Epstein-Barr virus (EBV) antibodies were measured in blood samples from 1457 adults aged 25–90. Regression models were then used to determine the relationships between viral reactivation, age, gender, ethnicity and SEP.

Results—Individuals were significantly more likely to have higher antiviral antibodies (ie, reactivation) to both EBV and HSV-1 than one virus alone. Individuals in the lowest age group had less reactivation, whereas greater reactivation was observed in women and those with the least education. Compared to white non-Hispanics, Hispanics and black non-Hispanics experienced more viral reactivation. These relationships remained strong after controlling for sociodemographic factors as well as smoking status, body mass index and physical activity.

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Competing interests None.

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Conclusions—These results demonstrate that herpesvirus reactivation is associated with variables such as age, gender, ethnicity and education, and may play a role in poorer health outcomes in both younger and older adults.

INTRODUCTION

Herpesviruses commonly establish latent infections in adults. The best known members of this family include herpes simplex virus (HSV), varicella zoster virus (VZV), and Epstein-Barr virus (EBV). HSV-1 infects 70–80% of all adults worldwide and is classically associated with oropharyngeal lesions such as cold sores, pharyngitis and tonsillitis.[1] EBV, infecting over 85% of adults, is the causative agent of infectious mononucleosis, Burkitt's lymphoma, undifferentiated nasopharyngeal carcinoma and diffuse polyclonal B cell lymphoma.[2] VZV causes chickenpox on primary infection and remains latent thereafter, reactivating in episodes of zoster or 'shingles'.[3]

In previously infected (seropositive) individuals, antiviral IgG antibodies are always present and are tightly regulated by the immune system due to control over viral reactivation by cytotoxic T cells.[2] Therefore, levels of herpesvirus antibodies in healthy individuals are extremely stable. However, a dysfunction of the immune system permits viral reactivation and leads to increased levels of antiviral antibodies. For instance, the well-documented age-related declines in cellular immunity are associated with increased herpesvirus antibodies.[4–6] Several studies have also demonstrated that stress down-regulates T cell immunity, resulting in productive cycles of viral replication and increased production of antiviral antibodies.[7–11]

Increased anti-EBV antibodies, increased transcription of EBV early and late replicative proteins, and increased viral load (ie, EBV DNA) have recently been found in blood from older adults (≥65 years of age).[12] Notably, viral DNA levels in samples from younger control subjects (≤55 years old) were at or below detection and viral gene transcription was mostly absent; these results corresponded with low anti-EBV antibody titres. Moreover, increased antiviral antibodies have been observed only in subjects who were also positive for viral DNA.[13] Thus, prior studies of viral DNA detection support the notion that elevated antiviral IgG antibodies are due to increased reactivation and not simply to duration of infection; this is also underscored by the half-life (23 days) of circulating IgG.[14]

Although exposure to herpesviruses is ubiquitous, factors such as old age and low socioeconomic position (SEP) have been consistently associated with higher rates of seropositivity.[1516] The latter is significant because SEP represents one of the most important risk factors for chronic disease, disability and mortality. Individuals with low SEP have a greater risk of infection,[17] and a higher incidence of disease risk markers[18] and all-cause mortality.[19] Recently, Dowd and coworkers[20] found lower educational levels correlated with higher anti-HSV-1 and anti-CMV antibodies in a group of older Mexican Americans. These data suggest that levels of herpesvirus antibodies may be associated with ethnicity and SEP, possibly through stress-mediated downregulation of cellular immunity; it is unknown if these observations can be extended across community-based studies that include younger groups as well.

In the present study, anti-EBV and anti-HSV-1 antibodies were measured in 1457 adults aged 25–90 and their relationship with various socio-demographic characteristics was determined. Given the potential pathway between SEP, stress and viral reactivation, it was hypothesised that viral reactivation would be more common among ethnic minorities, older adults and those with lower education.

MATERIALS AND METHODS

Subjects

Data for this study come from the Texas City Stress and Health Study, an ongoing assessment of risk, coping, stress and health in a tri-ethnic community living near a petrochemical hazard in Texas City, Texas. This study set out to explore sociobiological patterns in a population living close to a cluster of petrochemical plants, with a focus on Hispanics.[21,22] First, an exhaustive listing of housing units (HUs) was performed. Next, HUs were classified as Hispanic (defined as at least one adult who self-identified as Hispanic) or other households. Next, HUs were divided into three ethnic strata: Mexican Americans aged 25–64, Mexican Americans aged 65 and over, and non-Hispanics. HUs in each stratum were selected, including all Hispanic HUs and one in eight non-Hispanic HUs. Finally, one adult was randomly selected per household among Mexican Americans aged 25–64 and among non-Hispanics, and all Mexican Americans aged 65 and over. Listing, enumeration and interviewing followed standard US Census Bureau Current Population Survey methods with appropriate local modifications. The total sample for the survey portion of the data was 2706.

Blood samples were drawn from participants between 08:00 and 11:00. To measure biomarkers, blood was drawn into EDTA tubes. Plasma was obtained after centrifugation and stored in 1-millilitre aliquots at −70°C until testing. The institutional review board at the University of Texas Medical Branch approved the study protocol, and written informed consent was obtained from all participants.

Measurement of antiviral antibodies

Antiviral antibody titres were determined by indirect immuno-fluorescence as previously described.[23,24] Commercially prepared substrate slides and control sera (Microgen Laboratories, La Marque, Texas, USA, and Bion Enterprises, Park Ridge, Illinois, USA) were used to determine IgG antibody titres to EBV-viral capsid antigen (VCA), EBV-early antigen (EA) and HSV-1. Of note, proteins of the VCA complex are late antigens released during productive viral replication, whereas incomplete reactivation is indicated by increased antibodies to the EA complex. Plasma was tested in the following dilutions for EA: 1:10, 1:40, 1:160 and 1:640. The VCA and HSV-1 tests used 1:10, 1:40, 1:160, 1:640, 1:2560 and 1:10 240. For VCA, EA and HSV-1 IgG antibody determinations, 30 microlitres of titrated sera were pipetted onto spot slides and incubated for 30 min at room temperature. After incubation, the spot slides were rinsed for 5 min in PBS. The secondary antibody used was antihuman IgG conjugated with fluorescein isothiocynate. Evans blue was used as a counterstain. After a second incubation (30 min at room temperature), slides were washed, lightly blotted and mounted with mounting medium. All specimens were batch-analysed and

read blind-coded, and the SE of the assay was ±1 dilution. The endpoint titre was determined as the highest dilution of serum demonstrating immunofluorescent-positive cells.

Statistics

Analysis of variance and Student t tests were conducted on age, education, gender and ethnic variables for continuous antibody titres to EBV-VCA, EBV-EA and HSV-1. Reactivation or 'positives' were then defined by establishing cut-offs for each antibody titre based on prior results[12,13,23]; VCA and HSV-1 were defined as titres ≥1280, whereas for EA it was ≥80. Contingency tables were then examined with respect to demographic differences in per cent of respondents positive for EBV-VCA, EBV-EA and HSV-1. Expected and observed frequencies were also compared for the combined positives of EBV-VCA, EBV-EA and HSV-1. Next, logistic regression was utilised to address the associations between key social disparity variables and the likelihood of being positive for EBV-VCA, EBV-EA and HSV-1, while adjusting for sociodemographic factors, smoking status, physical activity and body mass index (BMI). Finally, logistic regression was used to examine the associations between social disparity variables and the odds of testing positive for ≥1 and ≥2 combinations, while adjusting for sociodemographic factors, smoking status, physical activity and BMI. Analyses were performed using STATA (Version 9.2, StataCorp LP).

RESULTS

Table 1 shows the main characteristics of the study population. The mean age of study subjects was 48.9 years; 58.4% were women, and 52% were Hispanic, whereas black non-Hispanics and white non-Hispanics made up 10.3% and 36.8% respectively. Of the 1457 participants, 38% had less than a high school education, 31% had equivalent to a high school education and ~31% had greater than a high school education. White non-Hispanics had the highest education levels (43.3% greater than high school) followed by black non-Hispanics (32.7%) and Hispanics (23.1%). Blood samples were received from 54% of participants (n= 1457); the remainder of the subjects declined to participate in the blood sampling. Analyses revealed no statistically significant variations in mean educational levels, percentage with insurance, or marital status between subjects who participated in the blood draws and those who did not. However, the study sample had a higher percentage of women ($p<0.03$), a lower percentage of black non-Hispanic ($p<0.01$), lower mean perceived physical health ($p<0.001$), and higher mean levels of chronic conditions ($p<0.01$).

Regarding antiviral antibody titres, nine of the subjects had a titre <10 for HSV-1 (range <10–5120). For EA, 238 subjects had a titre <10 (range <10–160), whereas for VCA only three of the subjects had a titre <10 (range <10–5120). Table 2 indicates the mean levels of VCA, EA and HSV-1 by age, gender, education and ethnicity. Mean VCA titres for ages <45, 45–64 and >64 were 684, 861 and 923, respectively, with the youngest age group (<45) being significantly lower than both older age groups. Mean EA titres for the three age groups were 19, 24 and 28, respectively, with the younger groups being significantly different from the group aged >64. Mean HSV-1 titres for the three groups were 795, 950 and 1039, respectively, with the youngest group being significantly lower than the older groups. Association was also evaluated with age by looking at the percentage of subjects by

age with elevated levels of antiviral titres, indicative of recent reactivation. Table 2 shows the same trend of per cent positive reactivation for each viral marker. In other words, the youngest age group has a significantly lower percentage of respondents testing positive. Furthermore, when analysed by decade, there were significant associations between increased age and per cent positive for EA, VCA and HSV-1 ($p<0.001$; results not shown).

Table 2 also shows significant differences in antiviral antibody titres by education, gender and ethnic groups. Individuals with more than a high school education had lower mean HSV-1 antibodies and per cent positives than those with a high school education or less, and those with a high school education had significantly lower HSV-1 antibodies (mean and percentage) than those with less than a high school education. Subjects with more than a high school education had higher mean EA levels than those with a high school education ($p<0.05$). No significant changes were found for VCA across the three groups.

Women had a significantly higher percentage and higher mean levels of VCA than men. For EA, only mean levels were significantly higher in women. Mean and percentage of HSV-1 titres were also higher in women but the difference was not statistically significant. Black non-Hispanics had significantly higher mean EA antibody titres than Hispanics, whereas white non-Hispanics had significantly lower mean HSV-1 antibody titres than black non-Hispanics or Hispanics; the percentage of anti-HSV-1 antibodies were significantly higher in black non-Hispanics as compared to Hispanics.

Table 3 shows the results of logistic regression analysis of the effect of demographic variables on likelihood of positivity on VCA, EA and HSV-1. Being female was associated with an increase in the odds of positive VCA, whereas being <45 years of age (compared to >64) was associated with a decrease in odds. For EA, being female was associated with an increase in the odds of testing positive, whereas being <45 years old was associated with a decrease in the odds. For HSV-1 positivity, being <45 years old was associated with a decrease in the odds, and being black non-Hispanic or Hispanic or having a high school degree or less was associated with increased odds.

Next, it was examined whether subjects with an elevated titre for one viral marker were more likely to have elevated titres for other viral markers. Results were analysed as if the three tests were independent (table 4). The occurrence of individuals with one positive test was less than expected, whereas the occurrence of individuals with two or three positive tests was greater than expected. Altogether, these data demonstrate that these viral markers are not independent.

Finally, multivariate logistic regression analyses (table 5) were performed to determine the predictors of being positive on (1) one or more and (2) two or more viral markers. For one or more positive viral markers, women, black non-Hispanics and those less educated had an increase in odds, whereas being young was associated with a decrease in the odds. Similarly, women and black non-Hispanics were associated with an increase in odds of having two or more positive viral markers, whereas being young was associated with a decrease in the odds.

DISCUSSION

This is the first study of which the authors are aware that demonstrates an association between reactivation of latent herpesviruses and SEP using a community-based study. Initially, a significant correlation was demonstrated between EBV and HSV-1 antibodies and age. This is important because the age-related correlations in antiviral antibody titres serve as an 'internal control', thus validating the present assay measurements across a large data set including a wide range of ages. Also, these results confirm prior findings of age-related increases in herpesvirus reactivation,[4,12] and further support the concept that the aged immune system can no longer control a herpesvirus reactivation now characterised as chronic rather than latent.

Reactivation, or 'positives', were then defined as one titre greater (ie, VCA and HSV-1 titres ≥1280; EA titres ≥80) than the highest titre found in control subjects.[12] The present results reflect both individual and social differences in viral reactivation. In addition, it was found that subjects who experienced reactivation were more likely to be positive for both viral markers, suggesting a generalised decline in cellular immunity as opposed to a specific virus-associated event. These results are consistent with patterns of higher levels of herpesvirus antibodies in aged individuals with lower levels of education.[20] The exception was EA antibodies, which were highest in individuals with more than a high school education; lower levels of EA antibodies were expected in this group as it was hypothesised that they might experience lower stress. It is unlikely that recent or primary infection accounted for the elevated EA antibodies as anti-EBNA IgG antibodies were also detected in these samples indicative of past infection (RP Stowe *et al* 2009, unpublished data). However, one possible explanation is incomplete or 'abortive' reactivation,[10] as VCA antibodies (which reflect productive virus replication) were not elevated in this group.

Prior studies assessed the presence or absence of antiviral antibodies (ie, seropositivity) in order to correlate with SEP,[15,16] and these results could be attributed to poorer hygiene and increased exposure to viral pathogens. In contrast, the present study addressed the effects of age, gender, ethnicity and SEP on immune responses to herpesviruses using quantitative measures (ie, antibody titres) in individuals previously infected with EBV and HSV-1. Thus, the quantitative nature of the present study allowed determination of subclinical reactivation and immune responses to these highly prevalent viruses and represents an improvement over previous studies.

Ethnic differences in HSV-1 infection were found in the Third National Health and Nutrition Examination Survey (NHANES),[15] which revealed that 64.7% of white non-Hispanics were infected whereas 85.1 and 74.1% of Hispanics and black non-Hispanics were infected respectively. The present subjects showed a much higher HSV-1 infection rate (ie, >90%) for all three groups across all age ranges; this included infection by EBV. White non-Hispanics had less HSV-1 reactivation than black non-Hispanics or Hispanics, whereas Hispanics had the lowest VCA and EA antibodies. The findings related to lower EBV antibodies in Hispanics were unexpected. However, further investigation is needed as differences in seropositivity were found between US and foreign-born Hispanics in the Third NHANES,[15] and a large percentage of Hispanics in the present study were foreign-

born. Notably, black non-Hispanics had much greater levels of all three antiviral antibodies. In particular, logistic regression analyses showed that black non-Hispanic were more likely to have one or more positive viral markers. It is possible that genetic factors may play a role in immune regulation of black non-Hispanics.[25]

Significantly higher viral reactivation was observed in women, particularly increased levels of anti-EBV antibodies. This agrees with prior studies reporting increased levels of EBV-VCA in women.[2627] Notably, the present data parallel other results of increased levels of inflammatory markers in women and black non-Hispanics.[2829] Indeed, recent reports have suggested a link between herpesviruses and inflammation. Elevated levels of cytomegalovirus (CMV) antibodies have been associated with increased interleukin (IL)-6 and tumour necrosis factor (TNF)α levels in older adults[30–32] and EBV-encoded dUTPase has been shown to upregulate TNFα, IL-1β, and IL-6.[3334] EBV and CMV infection also result in a clonal expansion of virus-specific CD8+ T cells.[1235–38] Thus, activation or an increase in virus-specific CD8+ T cells, as well as direct interaction with viral antigens, may increase levels of circulating inflammatory cytokines.

Although measures of stress in this study were not reported, psychosocial stress may have been a factor. In a study of West Point Military Cadets, Kasl and coworkers[39] found that psychosocial stress was a strong predictor of the onset and severity of infectious mononucleosis caused by EBV. Both acute and chronic stress are associated with reactivation of genital and oral HSV.[40–42] McKinnon and coworkers[43] found that residents surrounding the Three Mile Island nuclear powerplant area, the site of a serious accident in 1979, had decreased cytotoxic T lymphocytes and NK cells and higher antibody titres to latent HSV-1 and CMV. In academic models of stress, medical students had higher antibody titres to latent EBV compared to control subjects, but not to poliovirus type-2 (a non-latent virus).[101144] They also had a decreased virus-specific memory T lymphocyte response.[9] It is thought that individuals with lower education and lower income are more frequently faced with acute and chronic stressors through their physical, cultural and financial environments,[28] and the present findings related to demographic and socioeconomic differences are consistent with these beliefs.

In conclusion, the present results extend those from Dowd and coworkers[20] and provide a potential pathway through which individuals may experience poorer health outcomes. Evidence was found in this population-based sample that age is an important correlate of higher levels of VCA, EA and HSV-1 antibodies. In addition, lower education is associated with higher HSV-1 antibodies, whereas being female is associated with higher odds of testing positive (ie, reactivation) for EBV. Furthermore, being black non-Hispanic and Hispanic are associated with testing positive for HSV-1. Future studies are needed to clarify the link between, herpesviruses, demographic and SEP, disease and healthy ageing.

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What is already known on this subject

- Recent studies suggest a strong relationship between stress and increased levels of antibodies, possibly through stress-mediated downregulation of cellular immunity.
- Although rates of infection are known to be affected by socioeconomic status, there is a paucity of data demonstrating a link between viral reactivation, ethnicity and socioeconomic status.

What this study adds

- Variables such as age, gender, ethnicity and education were found to be associated with elevated levels of antiviral antibodies indicative of viral reactivation.
- Viral reactivation may be a promising in vivo indictor of immune function and play a role in poorer health outcomes in both younger and older adults.

Policy implications

- These results extend previous studies to provide a potential pathway through which individuals may experience poorer health outcomes.
- Findings related to demographic and socioeconomic differences are consistent with the belief that individuals with lower education and income are more frequently faced with acute and chronic stressors through their physical, cultural and financial environments.

Table 1

Main characteristics of the study population (n=1457)

Characteristic	Overall N=1457	White N=536	Hispanic N=757	Black N=150
Age, mean (SD)	48.9 (16.0)	55.6 (15.6)	49.2 (15.8)	50.9 (15.0)
Female, %	58.4	55.2	62.2	67.3
Education, %				
<12 years	37.8	20.6	52.1	27.3
12 years	31.1	36.0	24.9	40.0
≥12 years	31.1	43.3	23.1	32.7

Table 2

Mean antibody titres (SD) and per cent positive for EBV-VCA, EBV-EA and HSV-1 (n=1457)

	EBV-VCA		EBV-EA		HSV-1	
	Mean (SD)	**% Positive**	**Mean (SD)**	**% Positive**	**Mean (SD)**	**% Positive**
Age						
<45 years	683.9 (794.5)*	12.1*	19.1 (17.8)*	0.7*	795.4 (750.0)*	18.7*
45–64 years	860.9 (980.1)	17.3	24.3 (26.2)†	2.6	950.0 (838.8)	25.6
>64 years	922.8 (1021.6)	18.7	27.8 (32.6)	5.1	1039.3 (859.2)	31.7
Education						
<12 years	817.8 (933.9)	16.1	22.4 (25.2)	2.2	1014.2 (861.1) ‡ §	28.6‡
12 years	835.8 (947.8)	16.9	21.7 (23.8) ‡	2.0	917.2 (768.3) ‡	26.6
>12 years	769.9 (899/8)	13.9	25.5 (27.0)	3.3	795.6 (789.7)	17.8
Gender						
Female	848.4 (932.0)	17.3	24.9 (27.9)	3.1	931.6 (820.5)	25.2
Male	745.7 (917.8)¶	13.1¶	20.5 (20.6) ¶	1.6	889.6 (808.6)	23.5
Ethnicity						
Hispanic	778.3 (906.8)	14.7	21.8 (23.5)**	2.0	970.8 (838.9)	26.2**
Black	874.0 (911.0)	18.9	27.6 (28.9)	3.3	1056.5 (914.1)	32.0
White	830.3 (963.8)	16.0	23.4 (25.5)	2.6	798.8 (742.7)** ††	20.2

EBV-EA, Epstein-Barr virus-early antigen; EBV-VCA, Epstein-Barr virus-viral capsid antigen; HSV, herpes simplex virus. % Positive defined as ≥1280 for HSV-1 and VCA and ≥80 for EA.

*Significantly different (p<0.05) from 45–64 and 65+.

†Significantly different (p<0.05) from 65+.

‡Significantly different (p<0.05) from >12 years.

§Significantly different (p<0.05) from 12 years.

¶Significantly different (p<0.05) from women.

**Significantly different (p<0.01) from black non-Hispanic.

††Significantly different from Hispanic (p<0.01).

Table 3

Logistic regression results for predictors of positive EBV-VCA, EBV-VA and HSV-1 (n=1457)[*] [†]

	EBV-VCA		EBV-EA		HSV-1	
Demographic variables	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age						
<45 years	0.55	0.37 to 0.83	0.18	0.06 to 0.56	0.45	0.32 to 0.64
45–64 years	0.85	0.58 to 1.23	0.69	0.31 to 1.52	0.78	0.56 to 1.07
≥65 years	1.00		1.00		1.00	
Education						
<12 years	1.21	0.82 to 1.79	0.65	0.26 to 1.58	1.65	1.18 to 2.32
12 years	1.24	0.85 to 1.81	0.61	0.26 to 1.48	1.63	1.17 to 2.27
>12 years	1.00		1.00		1.00	
Female	1.41	1.02 to 1.96	2.59	1.12 to 5.98	1.07	0.82 to 1.41
Ethnicity						
Hispanic	0.87	0.61 to 1.22	0.95	0.42 to 2.18	1.40	1.04 to 1.89
Black non-Hispanic	0.99	0.60 to 1.63	1.39	0.47 to 4.08	1.80	1.18 to 2.74
White non-Hispanic	1.00		1.00		1.00	

EBV-EA, Epstein-Barr virus-early antigen; EBV-VCA, Epstein-Barr virus-viral capsid antigen; HSV, herpes simplex virus.

[*] ORs presented (95% CI).

[†] Models adjusted for smoking, body mass index and physical activity.

Table 4

Comparison of expected versus observed values for viral reactivation combinations

	Expected	Observed
All negatives	911.40	964
Only HSV	295.27	248
Only VCA	169.48	125
Only EA	22.89	12
HSV+VCA	54.91	94
HSV+EA	7.41	13
VCA+EA	4.26	7
HSV+VCA+EA	1.38	4

EA, early antigen; HSV, herpes simplex virus; VCA, viral capsid antigen. The probability of positive on HSV is 0.2447 (p1); the probability of positive on VCA is 0.1567 (p2); and the probability of positive on EA is 0.0245 (p3).

Goodness of fit test: $\chi^2 = 66.25$, $p<0.0001$.

Table 5

Logistic regression results for predictors of one or more positive and two or more positive for EBV-VCA, EBV-VA and HSV-1 (n=1457)[*] [†]

	1+ Positive		2+ Positive	
Demographic variables	**OR**	**95% CI**	**OR**	**95% CI**
Age				
<45 years	0.43	0.31 to 0.59	0.42	0.24 to 0.72
45–64 years	0.79	0.59 to 1.07	0.67	0.41 to 1.09
≥65 years	1.00		1.00	
Education				
<12 years	1.42	1.05 to 1.92	1.51	0.87 to 2.61
12 years	1.42	1.06 to 1.91	1.47	0.85 to 2.52
>12 years	1.00		1.00	
Female	1.26	0.99 to 1.61	1.46	0.93 to 2.29
Ethnicity				
Hispanic	1.10	0.84 to 1.43	1.31	0.80 to 2.12
Black non-Hispanic	1.42	0.96 to 2.10	1.74	0.91 to 3.34
White non-Hispanic	1.00		1.00	

EBV-EA, Epstein-Barr virus-early antigen; EBV-VCA, Epstein-Barr virus-viral capsid antigen; HSV, herpes simplex virus.

[*] ORs presented (95% CI).

[†] Models adjusted for smoking, BMI and physical activity.