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Insight into Hepatitis B Prevalence and Risk Factors Among Vietnamese Americans: A Cross-Sectional Community-Based Screening Study

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ABSTRACT

Objectives: The aims of our study were to describe current hepatitis B prevalence among Vietnamese Americans and to examine predictors of hepatitis B risk in this specific ethnic community.

Design: Cross-sectional study.

Setting: This study was based on hepatitis screening community events in Southern California.

Participants: 2,508 Vietnamese Americans in Southern California.

Outcome Measures: Serological tests for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and total hepatitis B core antibody (anti-HBc) were used to classify participants as one of four hepatitis B infection statuses: currently infected, previously infected, susceptible, or immune due to a previous hepatitis B vaccination.

Results: Across 2,508 participants, 9.0% were currently infected with hepatitis B and 17.7% were at risk for hepatitis B. Females and those reporting a previous hepatitis B vaccination were at significant decreased risk of hepatitis B (OR=0.48, 95%CI 0.33-0.69 and OR=0.53, 95%CI 0.31-0.93, respectively) whereas those born outside of the United States and with a family history of the disease showed substantial increased risk (OR=13.36, 95%CI 1.62-110.05 and OR=4.68, 95%CI 2.66-8.22, respectively). Among those who reported a previous hepatitis B vaccination, less than half (42.9%) possessed the protective antibodies that result from a hepatitis B vaccination.

Conclusions: Vietnamese Americans remain disproportionately burdened by hepatitis B. Public health efforts that focus on improving hepatitis B awareness and vaccination knowledge and that are tailored to specific high-risk subgroups, such as immigrants and those with infected family members, could help in addressing the disease's burden in this high-prevalence population.

INTRODUCTION

Hepatitis B is an important public health issue affecting more than 300 million people worldwide. (1) It is associated with substantial increased risk of severe liver diseases including liver cancer, which is the fifth and seventh leading cause of cancer death among males and females, respectively, and the fastest growing cause of cancer death in the United States (U.S.). (2, 3) Although the U.S. is considered a low-prevalence region for hepatitis B, the number of infected people is expected to grow due to immigration from endemic regions, particularly in Asia. (4, 5)

Asian Americans were the fastest growing racial group in the U.S. over the last decade. (6) They also have the highest rate of hepatitis B, accounting for more than 50% of all U.S. cases. (7-9) However, Asian Americans are often underrepresented in population-based hepatitis B studies and hence aggregated with other racial groups. (9, 10) They also constitute a heterogeneous population, yet most studies evaluate Asian Americans as a single group despite known ethnic-specific variation in hepatitis B's burden. (8)

Vietnamese Americans have one of the highest prevalences of hepatitis B, ranging from 7% to 14%; they also have high incidence and mortality rates of liver cancer. (8, 11, 12) In a recent study by Pham et al, incidence of liver cancer among Vietnamese American males was eight times higher than non-Hispanic white males and more than twice that of males of other Asian ancestries. (13) The study also observed little change in liver cancer incidence among Vietnamese American males and significant increasing rates among Vietnamese American females over the last three decades. (13) Since hepatitis B is an underlying cause of liver cancer and Vietnamese Americans are the second fastest growing Asian ethnic group in the U.S., there is a critical need to better understand hepatitis B and its risk factors in this subpopulation. (14)

Our study addresses this important area of research by examining hepatitis B specifically in Vietnamese Americans in Southern California, which is home to the highest number of Vietnamese Americans. (15) Only one study to our knowledge has examined hepatitis B in Vietnamese Americans in this geographic region using data from 2008 to 2010. (16) We have provided an updated evaluation using comprehensive serological and questionnaire data from over 2,500 Vietnamese Americans. This constitutea one of the largest studies of hepatitis B in the Vietnamese American community to date.

METHODS

Study Population

This cross-sectional study was based on a series of free hepatitis screening community events in Orange County, California and Los Angeles County, California organized by the Vietnamese American Cancer Foundation (<http://www.vacf.org/>) from February 2011 to November 2017. The Vietnamese American Cancer Foundation is a non-profit organization located in Fountain Valley, California whose mission is to educate and increase awareness of hepatitis and cancers among the Vietnamese community. Their hepatitis screening events were advertised in Vietnamese radio and television programs and newspapers as well as through community referral. Because some individuals participated in multiple screening events, duplicates were excluded from the analysis, resulting in 3,264 unique participants. While all who attended the events and desired testing were screened, those who did not report a Southern Californian residence (N=89) or a Vietnamese ethnicity (N=599) were excluded. In addition, we only included those with complete, determinate hepatitis B serological testing results, hence our final population was 2,508 participants.

Data Ascertainment

All participants attending the screening event were given a questionnaire in Vietnamese or English by trained staff that included questions regarding their demographics, risk factors, and relevant hepatitis B knowledge, such as one's hepatitis B status as well as the statuses of household and family members. All questionnaire data collected were self-reported. In addition, participants were given a 30-minute lecture on hepatitis B by a physician specializing in liver diseases at the event. Because the primary language for most screening participants was Vietnamese, the lecture was delivered in Vietnamese. However, lecture slides were presented in English as well. Participants' blood was drawn by trained phlebotomists following the lecture and later tested for the hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and total hepatitis B core antibody (anti-HBc). Follow-up events were organized by the Vietnamese American Cancer Foundation when screening results were ready to be disseminated. At that time, a physician explained the results to the participants, answered any questions as well as discussed next steps. For those unable to attend, results were mailed with a detailed letter explaining each serological test. Staff also contacted these individuals to ensure they received proper follow-up care if needed.

Statistical Analysis

We considered all participants with positive HBsAg and anti-HBc tests to be currently infected with hepatitis B. In addition, those who had an isolated positive anti-HBs test were considered immune due to having been previously vaccinated. Participants who had an isolated positive anti-HBc test or positive anti-HBs and anti-HBc tests were considered as having a past

hepatitis B infection. Lastly, participants who screened negative for all three tests were considered at risk or susceptible to hepatitis B.

Descriptive statistics in percentages were used to characterize the participants with regard to demographics, including age (<40, 40-49, 50-59, 60-69, 70+ years), gender (male/female), annual household income (<\$10,000, \$10,001-\$30,000, \$30,001+), education (less than high school, high school graduate, some college or technical/vocational training, college graduate), marital status (single/married), health insurance status (yes/no), and U.S. birth status (U.S. born/non-U.S. born) as well as relevant hepatitis B information, including family history of hepatitis B (yes/no) and personal history of hepatitis B vaccination (yes/no). A Chi-square test or Fisher’s exact test (when one or more cells had an expected frequency of five or less) was used to determine whether factors differed across the four hepatitis B statuses (past infection, immunity from vaccination, currently infected, susceptible). This analytic approach was also used to identify factors associated with risk of hepatitis B (i.e. comparing those currently infected to those susceptible). Characteristics found to be associated with risk of hepatitis B at a p-value of ≤ 0.10 were fit into a multivariate logistic regression model to quantify each factor’s effect on risk of hepatitis B using an odds ratio (OR) and a 95% confidence interval (CI). Missing categories were created for all variables and modeled where appropriate. To ensure our selection of significant factors in the fully adjusted model was not driven by differences in the missing categories, sensitivity analyses were conducted excluding the missing. Because the overall findings did not change with and without the missing categories, the results with the missing categories are presented.

All tests of statistical significance were two-sided. The analyses were performed using SAS software, release 9.4 (SAS Institute, Inc., Cary, North Carolina). Statistical significance was considered at a p-value of ≤ 0.05 .

Patient and Public Involvement

The Vietnamese American Cancer Foundation organized hepatitis screening community events in Orange County, California and Los Angeles County, California every year that were free and open to the public. Participants at these screening events completed a questionnaire and had their blood drawn, which was tested for hepatitis B serology. No specific patient population was included.

RESULTS

Among the 2,508 participants, 9.0% were currently infected with hepatitis B (N=225) and 17.7% were at risk or susceptible to hepatitis B (N=443). In addition, close to 46% had been previously infected (N=1,151) and approximately 27% were immune due to having received a hepatitis B vaccination (N=689) (Table 1).

The majority of participants were female (55.5%), 50 years of age or older (59.0%), and married (64.2%) with no more than a high school education or equivalent (53.1%) and living in a household with an annual income of less than \$30,000 (64.7%); almost all participants were born outside of the U.S. (96.2%) (Table 2). When characteristics were examined across the four hepatitis B statuses, significant differences in gender ($p=0.02$), age ($p<0.0001$), education ($p=0.004$), marital status ($p<0.0001$), U.S. birth status ($p<0.0001$), family history of hepatitis B ($p=0.0001$), and personal history of hepatitis B vaccination ($p<0.0001$) were observed (Table 2).

When comparisons were made between only those susceptible and those currently infected, we found gender ($p=0.006$), annual household income ($p=0.021$) as well as whether the participant was born outside of the U.S ($p=0.006$), had a family history of hepatitis B ($p<0.0001$), and was previously vaccinated against hepatitis B ($p=0.017$) to be statistically significantly associated with hepatitis B risk (Table 2). We also conducted a subset analysis among those born outside of the U.S. to examine whether year of entry into the U.S. would differentially affect risk, however no significant association was found (data not shown).

When gender, age, income, family history of hepatitis B, personal history of hepatitis B vaccination, and U.S. birth status were jointly modeled along with year of screening, females were at a 52% reduced risk of hepatitis B relative to males (OR=0.48, 95% CI 0.33-0.69; Table 3). In addition, those who reported a previous hepatitis B vaccination were at a 47% reduced risk in comparison to those who did not (OR=0.53, 95% CI 0.31-0.93; Table 3). However, those born outside of the U.S. as well as those with a family history of hepatitis B were at substantial increased risk (OR=13.36, 95% CI 1.62-110.05 and OR=4.68, 95% CI 2.66-8.22, respectively; Table 3). In addition, there appeared to be increased risk after age 40 (ORs=1.40, 1.58, 1.54 for 40-49, 50-59, 60-69 years, respectively) until age 70 (OR=0.76) although none of the effect estimates were statistically significant (Table 3).

DISCUSSION

Although the literature recognizes Asian Americans as having the highest rate of hepatitis B in the U.S., the overall Asian population is diverse with variations in disease burden by ethnicity. (7, 8) For this reason, our report focuses specifically on Vietnamese Americans who have high hepatitis B prevalence. (8) Using data from community screening events from 2011 to 2017, 9.0% of participants were currently infected with hepatitis B; this is similar to the 8.8%

prevalence determined by Nguyen et al's study of data spanning 2008 to 2010, indicating little change in disease prevalence for this community. (16) Nguyen et al also observed 15.4% of their participants were at risk of hepatitis B, 53.8% had a past infection, and 21.9% were immune from vaccination; this is in comparison to our percentages of 17.7%, 45.9%, and 27.5%, respectively. (16) Given efforts to improve understanding of hepatitis B among the Vietnamese American community, it is not surprising that our updated evaluation shows a greater proportion with immunity from vaccination and a lower proportion with natural immunity via a past infection. However, we did observe a higher percentage of susceptible participants, which may be a result of increased awareness prompting those still at risk to undergo screening. This higher percentage could also reflect a growth in the number of at-risk Vietnamese Americans in the Southern California region, highlighting the need for continued hepatitis B public health efforts.

Not surprisingly, most participants whose serology indicated immunity from vaccination were those who reported having been previously vaccinated. However, among those who reported a previously vaccination, only 42.9% possessed protective antibodies with 13.6% still susceptible to hepatitis B and 4.8% currently infected with hepatitis B. This discrepancy between self-reported vaccination status and confirmed serology is an important issue and could be due to several reasons. First, participants may have inaccurately reported their vaccination status because they confused a vaccine for another disease with a vaccine for hepatitis B. The contrary may also be true; our data showed close to 20% of those who reported not having been previously vaccinated possessing protective antibodies that indicate previous immunization. Second, because the hepatitis B vaccine is given as a series of shots over a six-month time period, some participants may not have received all necessary shots and hence were not immunized, but thought they were. These reasons highlight the need for improved health

education and hepatitis B vaccination knowledge in the Vietnamese American community. Another explanation for why some participants who reported being vaccinated were currently infected may be due to the fact that they were already infected at the time of their vaccination. It is currently not standard clinical practice to test for hepatitis B prior to administering the vaccine, but this may be worthwhile to do particularly for high-risk individuals. (17)

Our study found those born outside of the U.S. to be over 13 times as likely to be infected with hepatitis B compared to those born in the U.S., a finding supported by another screening study by Kallman et al. (18) Given that these individuals are likely immigrants from Vietnam, they may lack knowledge regarding hepatitis B and hence are unaware of their infection status. There could also be a lack of health literacy or access to care due to financial, linguistic, and cultural barriers, which have been documented as contributing factors to health disparities among Asian American immigrants. (19-21) More culturally-tailored public health programs and interventions that aim to increase hepatitis B awareness and knowledge, particularly among Vietnamese Americans born outside of the U.S., are needed.

We identified family history as a significant predictor of hepatitis B risk, which is in line with other cross-sectional screening studies conducted in Vietnamese Americans and Asian Americans. (12, 17, 18) The substantial increased risk among those with a family history is not surprising given that hepatitis B is often transmitted from an infected mother to her baby during birth or through direct contact with blood, semen, or other bodily fluids from an infected person. We also identified gender as a significant predictor with females having a lower risk of hepatitis B than males, which may be a result of gender-specific health behaviors and perceptions. For example, females are generally more health conscious and hence may have higher levels of hepatitis B awareness and knowledge as well as greater use of hepatitis B services. (22, 23)

Males also tend to possess certain lifestyle factors that promote the adoption of more traditional masculine perspectives that underplay the importance of health-protective behaviors. (24, 25) For example, a Vietnamese American male who constructs masculinity as self-reliance or putting work ahead of all other responsibilities may not make time for self-care or seek routine health services, indicating a need to improve health education and outreach for males.

The strengths of our study include its large sample size as well as our primary focus on the Vietnamese American community. Our study also used serological tests for HBsAg, anti-HBc, and anti-HBs to accurately classify each participant's hepatitis B status. Many screening fairs have relied solely on HBsAg testing despite the need for anti-HBs and anti-HBc tests to properly identify those truly at risk. While our findings may not necessarily be generalizable to the entire Vietnamese American population, Southern California has the highest concentration of Vietnamese Americans in the U.S., making it the ideal region to study hepatitis B for this ethnicity. Other limitations of our study include lack of information on other factors that may affect hepatitis B risk as well as missing participant data for certain characteristics. These are often issues with questionnaires administered at screening fairs due to time constraints. We did conduct sensitivity analyses with and without the missing data and the overall results did not change. Lastly, our questionnaire data were based on self-report, which may result in misclassification as we noted for participants' hepatitis B vaccination status. However, there is little reason to believe that the misclassification would occur more or less often for those of a certain hepatitis B status, hence any bias would only be towards the null.

Overall, our study provides an updated evaluation on hepatitis B prevalence in the Vietnamese American community and identifies certain subgroups within it, particularly those born outside of the U.S. and those with a hepatitis B family history, who may be at increased risk

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2
3 and require targeted interventions. In addition, we observed important discrepancies between
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5 self-reported hepatitis B vaccination status and confirmed serological results, which highlight the
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7 need to improve hepatitis B vaccination knowledge among Vietnamese Americans and their
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9 health providers. Our comprehensive serological testing makes this a unique effort with findings
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11 that can inform strategies to address hepatitis B’s burden in the Vietnamese American
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TABLE 1. Percentage of screening participants by hepatitis B status

Serological Results	Interpretation	Number of Participants	Percent of Participants*
HBsAg- anti-HBs+/- anti-HBc+	Past infection	1,151	45.9%
HBsAg- anti-HBs+ anti-HBc-	Immunity from vaccination	689	27.5%
HBsAg- anti-HBs- anti-HBc-	Susceptible	443	17.7%
HBsAg+ anti-HBs+/- anti-HBc+	Currently infected	225	9.0%

Note: HBsAg = hepatitis B surface antigen; anti-HBs = hepatitis B surface antibody; anti-HBc = total hepatitis B core antibody

* Does not total 100% due to rounding.

TABLE 2. Characteristics of screening participants by hepatitis B status

Characteristic	Past Infection*	Immunity from Vaccination*	Susceptible*	Currently Infected*	P-value†	P-value**
Gender					0.02	0.006
Male	540 (46.9)	276 (40.1)	176 (39.7)	116 (51.6)		
Female	609 (52.9)	408 (59.2)	265 (59.8)	108 (48.6)		
Missing	2 (0.2)	5 (0.7)	2 (0.5)	0 (0.0)		
Age					<0.0001	0.09
<40 years	103 (8.9)	208 (30.2)	125 (28.2)	45 (20.0)		
40-49 years	232 (20.2)	143 (20.8)	108 (24.4)	62 (27.5)		
50-59 years	384 (33.4)	167 (24.2)	114 (25.7)	68 (30.2)		
60-69 years	304 (26.4)	120 (17.4)	63 (14.2)	39 (17.3)		
70+ years	126 (11.0)	50 (7.3)	33 (7.5)	11 (4.9)		
Missing	2 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)		
Annual Household Income					0.066	0.021
≤\$10,000	363 (31.5)	208 (30.2)	137 (20.9)	65 (28.9)		
\$10,001 to \$30,000	405 (35.2)	223 (32.4)	130 (29.4)	91 (40.4)		
\$30,001+	185 (16.1)	115 (16.7)	92 (20.8)	32 (14.2)		
Missing	198 (17.2)	143 (20.8)	84 (19.0)	37 (16.4)		
Education					0.004	0.24
Less than high school	260 (22.6)	104 (15.1)	87 (19.6)	39 (17.3)		
High school graduate	394 (34.2)	225 (32.7)	136 (30.7)	87 (38.7)		
Some college or technical/vocational training	190 (16.5)	128 (18.6)	77 (17.4)	40 (17.8)		
College graduate	223 (19.4)	178 (25.8)	113 (25.5)	44 (19.6)		
Missing	84 (7.3)	54 (7.8)	30 (6.8)	15 (6.7)		
Marital Status					<0.0001	0.31
Single	290 (25.2)	264 (38.3)	147 (33.2)	63 (28.0)		
Married	794 (69.0)	387 (56.2)	279 (63.0)	150 (66.7)		
Missing	67 (5.8)	38 (5.5)	17 (3.8)	12 (5.3)		
Health Insurance					0.075	0.20
No	331 (28.8)	190 (27.6)	137 (30.9)	85 (37.8)		

Yes	718 (62.4)	428 (62.1)	260 (58.7)	118 (52.4)	<0.0001	0.006
Missing	102 (8.9)	71 (10.3)	46 (10.4)	22 (9.3)		
Born Outside of the U.S.						
No	7 (0.6)	31 (4.5)	19 (4.3)	1 (0.1)	<0.0001	0.006
Yes	1130 (98.2)	644 (93.5)	415 (93.7)	223 (99.1)		
Missing	14 (1.2)	14 (0.6)	9 (2.0)	1 (0.1)		
Family History of Hepatitis B					0.0001	<0.0001
No	707 (61.4)	395 (57.3)	281 (63.4)	118 (52.4)		
Yes	116 (10.1)	69 (10.0)	37 (8.4)	44 (19.1)		
Missing	328 (28.5)	225 (32.7)	125 (28.2)	63 (28.5)	<0.0001	0.017
Previous Hepatitis B Vaccination						
No	662 (57.5)	263 (38.2)	245 (55.4)	150 (66.7)		
Yes	203 (17.6)	225 (32.7)	71 (16.0)	25 (11.1)		
Missing	286 (24.9)	201 (29.2)	127 (28.7)	50 (22.2)		
Total:	1,151	689	443	225		

* Number of participants (percent of participants); may not total 100% due to rounding.

† Chi-square p-value comparing all four hepatitis B statuses

** Chi-square p-value comparing those susceptible to hepatitis B to those currently infected with hepatitis B

TABLE 3. Odds ratio and 95% confidence intervals for the association between screening participant characteristics and risk of hepatitis B

Characteristic	Odds Ratio*	95% Confidence Interval	P-value
Gender			
Male	1.00	--	--
Female	0.48	0.33 – 0.69	<0.0001
Age			
<40 years	1.00	--	--
40-49 years	1.40	0.83 – 2.36	0.20
50-59 years	1.58	0.95 – 2.62	0.078
60-69 years	1.54	0.85 – 2.79	0.15
70+ years	0.76	0.32 – 1.77	0.52
Annual Household Income			
≤\$10,000	1.00	--	--
\$10,001 to \$30,000	1.32	0.86 – 2.03	0.35
\$30,001+	0.56	0.32 – 0.99	0.046
Born Outside of the U.S.			
No	1.00	--	--
Yes	13.36	1.62 – 110.05	0.016
Family History of Hepatitis B			
No	1.00	--	--
Yes	4.68	2.66 – 8.22	<0.0001
Previous Hepatitis B Vaccination			
No	1.00	--	--
Yes	0.53	0.31 – 0.93	0.023

* Adjusted for all other characteristics as well as year of screening

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CONTRIBUTORS

AWL, WJ, BN, and TVN contributed to the conception and design of the study. BN, DNH, JNH, and TVN contributed to the study’s data collection. AWL, WJ, EC, and PY contributed to statistical analysis and interpretation of the data. AWL, WJ, and EC drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

ETHICS APPROVAL

All data analyzed in this report had institutional ethics committee approval from California State University, Fullerton (research project number: HSR-17-18-515).

DATA SHARING STATEMENT

No additional data available.

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COMPETING INTERESTS

The authors have no competing interests to disclose.

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract Done
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found Done
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Done
Objectives	3	State specific objectives, including any prespecified hypotheses Done
Methods		
Study design	4	Present key elements of study design early in the paper Done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Done
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants Done
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Done
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Done
Bias	9	Describe any efforts to address potential sources of bias Done
Study size	10	Explain how the study size was arrived at Done
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Done
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding Done
		(b) Describe any methods used to examine subgroups and interactions Done
		(c) Explain how missing data were addressed Done
		(d) If applicable, describe analytical methods taking account of sampling strategy
		(e) Describe any sensitivity analyses Done
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Done
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Done
		(b) Indicate number of participants with missing data for each variable of interest Done
Outcome data	15*	Report numbers of outcome events or summary measures Done
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Done
		(b) Report category boundaries when continuous variables were categorized Done

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Done
Discussion		
Key results	18	Summarise key results with reference to study objectives Done
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Done
Generalisability	21	Discuss the generalisability (external validity) of the study results Done
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Done

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Insight into Hepatitis B Prevalence and Risk Factors Among Vietnamese Americans: An Analysis of Data from a Community-Based Screening Program

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ABSTRACT

Objectives: The aims of our study were to describe current hepatitis B prevalence among Vietnamese Americans and to examine predictors of hepatitis B risk in this specific ethnic community.

Design: Analysis of data from a community-based screening program.

Setting: This analysis was based on hepatitis screening community events in Southern California.

Participants: 2,508 Vietnamese Americans in Southern California.

Outcome Measures: Serological tests for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and total hepatitis B core antibody (anti-HBc) were used to classify participants as one of four hepatitis B infection statuses: currently infected, previously infected, susceptible, or immune due to a previous hepatitis B vaccination.

Results: Across 2,508 participants, 9.0% were currently infected with hepatitis B and 17.7% were at risk for hepatitis B. Females and those reporting a previous hepatitis B vaccination were at significant decreased risk of hepatitis B (OR=0.48, 95%CI 0.33-0.69 and OR=0.53, 95%CI 0.31-0.93, respectively) whereas those born outside of the United States and with a family history of the disease showed substantial increased risk (OR=13.36, 95%CI 1.62-110.05 and OR=4.68, 95%CI 2.66-8.22, respectively). Among those who reported a previous hepatitis B vaccination, less than half (42.9%) possessed the protective antibodies that result from a hepatitis B vaccination.

Conclusions: Vietnamese Americans remain disproportionately burdened by hepatitis B. Public health efforts that focus on improving hepatitis B awareness and vaccination knowledge and that are tailored to specific high-risk subgroups, such as immigrants and those with infected family members, could help in addressing the disease's burden in this high-prevalence population.

INTRODUCTION

Hepatitis B is an important public health issue affecting approximately 257 million people worldwide. (1) It is associated with substantial increased risk of severe liver diseases including liver cancer, which is the fifth and seventh leading cause of cancer death among males and females, respectively, and the fastest growing cause of cancer death in the United States (U.S.). (2, 3) Although the U.S. is considered a low-prevalence region for hepatitis B, the number of infected people is expected to grow due to immigration from endemic regions, particularly in Asia. (4, 5)

Asian Americans were the fastest growing racial group in the U.S. over the last decade. (6) They also have the highest rate of hepatitis B, accounting for more than 50% of all U.S. cases. (7-9) However, Asian Americans are often underrepresented in population-based hepatitis B studies and hence aggregated with other racial groups. (9, 10) They also constitute a heterogeneous population, yet most studies evaluate Asian Americans as a single group despite known ethnic-specific variation in hepatitis B's burden. (8)

Vietnamese Americans have one of the highest prevalences of hepatitis B, ranging from 7% to 14%; they also have high incidence and mortality rates of liver cancer. (8, 11, 12) In a recent study by Pham et al, incidence of liver cancer among Vietnamese American males was eight times higher than non-Hispanic white males and more than twice that of males of other Asian ancestries. (13) The study also observed little change in liver cancer incidence among Vietnamese American males and significant increasing rates among Vietnamese American females over the last three decades. (13) Since hepatitis B is an underlying cause of liver cancer and Vietnamese Americans are the second fastest growing Asian ethnic group in the U.S., there is a critical need to better understand hepatitis B and its risk factors in this subpopulation. (14)

Because some individuals were likely to have participated in multiple screening events, we only included those who participated in one event. We attempted to avoid duplicate entries by excluding those of the same sex and date of birth since VACF did not keep track of those who received multiple screenings from them. This exclusion resulted in 3,264 unique participants. While all who attended the events and desired testing were screened, those who did not report a Southern Californian residence (N=89) or a Vietnamese ethnicity (N=599) were excluded. In addition, we only included those who had confirmed serological testing results for the hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and total hepatitis B core antibody (anti-HBc), leaving us with a final population of 2,508 participants; all three serological tests are needed to properly differentiate those truly at risk of hepatitis B from those previously infected or immune via vaccination.

Data Ascertainment

All participants receiving VACF screening services were given a self-administered questionnaire in Vietnamese or English by trained staff. The questionnaire included questions regarding participants' demographics, whether family members have had hepatitis, their hepatitis B vaccination status, and knowledge of their own hepatitis infection status as well as the infection statuses of household members. Written consent was obtained at this time. Participants' blood was then drawn by trained phlebotomists and later tested for HbsAg, anti-HBs, and anti-HBc by various commercial laboratories in the Orange County region that partner with VACF; the majority of testing was done using Advia Centaur chemiluminescence immunoassay for determining hepatitis serology.

For VACF’s biannual screening events, participants attended a 30-minute lecture on hepatitis B by a physician specializing in liver diseases only after completion of the questionnaire to minimize any bias in their responses and prior to their blood draw. Because the primary language for most screening participants was Vietnamese, the lecture was delivered in Vietnamese, however lecture slides were presented in English as well. When the screening results were ready to be disseminated (typically within a month after each biannual screening event), VACF organized follow-up events in which they invited a physician to explain the results to the participants, answer any questions as well as discuss next steps. For those unable to attend (approximately 40-50%), results were mailed with a detailed letter explaining each serological test. Staff also contacted these individuals to link those who tested positive to insurance and/or medical assistance programs for treatment, navigate those at risk to their primary care physicians, community clinics, and/or local pharmacies for vaccinations, and encourage family members and partners to get tested. VACF was not able to organize follow-up events for those who received screening services at community health fairs and events (i.e. not VACF’s biannual screening events). However, similar efforts were taken to ensure these individuals received proper follow-up care if needed. Information regarding how many individuals actually received the necessary care was not available due to loss of follow-up.

All data were stored and managed in Community TechKnowledge (CTK) Apricot by Social Solutions, a cloud-based client management solution specifically designed for non-profit organizations; CTK Apricot is HIPAA-compliant and data could only be accessed by authorized users via password-protected accounts. The data analyzed in this report had institutional ethics committee approval from California State University, Fullerton.

Statistical Analysis

We considered all participants with positive HBsAg and anti-HBc tests to be currently infected with hepatitis B. In addition, those who had an isolated positive anti-HBs test were considered immune due to having been previously vaccinated. Participants who had an isolated positive anti-HBc test or positive anti-HBs and anti-HBc tests were considered as having a past hepatitis B infection. Lastly, participants who screened negative for all three tests were considered at risk or susceptible to hepatitis B.

Descriptive statistics in percentages were used to characterize the participants with regard to demographics, including age (<40, 40-49, 50-59, 60-69, 70+ years), gender (male/female), annual household income (<\$10,000, \$10,001-\$30,000, \$30,001+), education (less than high school, high school graduate, some college or technical/vocational training, college graduate), marital status (single/married), health insurance status (yes/no), and U.S. birth status (U.S. born/non-U.S. born) as well as relevant hepatitis B information, including family history of hepatitis B (yes/no) and personal history of hepatitis B vaccination (yes/no). A Chi-square test or Fisher's exact test (when one or more cells had an expected frequency of five or less) was used to determine whether factors differed across the four hepatitis B statuses (past infection, immunity from vaccination, currently infected, susceptible). This analytic approach was also used to identify factors associated with risk of hepatitis B (i.e. comparing those currently infected to those susceptible). Characteristics found to be associated with risk of hepatitis B at a p-value of ≤ 0.10 were fit into a multivariate logistic regression model to quantify each factor's effect on risk of hepatitis B using an odds ratio (OR) and a 95% confidence interval (CI). (17) Missing categories were created for all variables and modeled where appropriate. To ensure our selection of significant factors in the fully adjusted model was not driven by differences in the missing

hepatitis B statuses, significant differences in gender ($p=0.02$), age ($p<0.0001$), education ($p=0.004$), marital status ($p<0.0001$), U.S. birth status ($p<0.0001$), family history of hepatitis B ($p=0.0001$), and personal history of hepatitis B vaccination ($p<0.0001$) were observed (Table 2).

Because gender, age, income, family history of hepatitis B, personal history of hepatitis B vaccination, and U.S. birth status were statistically significantly associated with hepatitis B risk when comparing only those susceptible to those currently infected (Table 2), we jointly modeled those factors with year of screening and found females to be at a 52% reduced risk of hepatitis B relative to males (OR=0.48, 95% CI 0.33-0.69; Table 3). In addition, those who reported a previous hepatitis B vaccination were at a 47% reduced risk in comparison to those who did not (OR=0.53, 95% CI 0.31-0.93; Table 3). However, those born outside of the U.S. as well as those with a family history of hepatitis B were at substantial increased risk (OR=13.36, 95% CI 1.62-110.05 and OR=4.68, 95% CI 2.66-8.22, respectively; Table 3). We conducted a subset analysis among those born outside of the U.S. to examine whether year of entry into the U.S. would differentially affect risk, however no significant association was found (data not shown). Lastly, there appeared to be increased risk after age 40 (ORs=1.40, 1.58, 1.54 for 40-49, 50-59, 60-69 years, respectively) until age 70 (OR=0.76) although none of the effect estimates were statistically significant (Table 3).

DISCUSSION

Although the literature recognizes Asian Americans as having the highest rate of hepatitis B in the U.S., the overall Asian population is diverse with variations in disease burden by ethnicity. (7, 8) For this reason, our report focuses specifically on Vietnamese Americans who have one of the highest prevalences of hepatitis B. (8) Using data from community screening events from 2011 to 2017, 9.0% of participants were currently infected with hepatitis B; this is

similar to the 8.8% prevalence determined by Nguyen et al’s study of VACF data spanning 2008 to 2010, indicating little change in disease prevalence for this community. (16) Nguyen et al also observed 15.4% of their participants were at risk of hepatitis B, 53.8% had a past infection, and 21.9% were immune from vaccination; this is in comparison to our percentages of 17.7%, 45.9%, and 27.5%, respectively. (16) Given efforts to improve understanding of hepatitis B among the Vietnamese American community, it is not surprising that our updated evaluation shows a greater proportion with immunity from vaccination and a lower proportion with natural immunity via a past infection. However, we did observe a higher percentage of susceptible participants, which may be a result of increased awareness prompting those still at risk to undergo screening. This higher percentage could also reflect a growth in the number of at-risk Vietnamese Americans in the Southern California region, highlighting the need for continued hepatitis B public health efforts.

Not surprisingly, most participants whose serology indicated immunity from vaccination were those who reported having been previously vaccinated. However, among those who reported a previously vaccination, only 42.9% possessed protective antibodies with 13.6% still susceptible to hepatitis B and 4.8% currently infected with hepatitis B. This discrepancy between self-reported vaccination status and confirmed serology is an important issue and could be due to several reasons. First, participants may have inaccurately reported their vaccination status because they confused a vaccine for another disease with a vaccine for hepatitis B. The contrary may also be true; our data showed close to 20% of those who reported not having been previously vaccinated possessing protective antibodies that indicate previous immunization. Second, because the hepatitis B vaccine is given as a series of shots over a six-month time period, some participants may not have received all necessary shots and hence were not

immunized, but thought they were. These reasons highlight the need for improved health education and hepatitis B vaccination knowledge in the Vietnamese American community. Another explanation for why some participants who reported being vaccinated were currently infected may be due to the fact that they were already infected at the time of their vaccination. It is currently not standard clinical practice to test for hepatitis B prior to administering the vaccine, but this may be worthwhile to do particularly for high-risk individuals. (18)

Our study found those born outside of the U.S. to be over 13 times as likely to be infected with hepatitis B compared to those born in the U.S., a finding supported by another screening study by Kallman et al. (19) Given that these individuals are likely immigrants from Vietnam, they may lack knowledge regarding hepatitis B and hence are unaware of their infection status. Unlike the U.S. where there is a multipronged strategy for hepatitis B prevention (e.g. antenatal screenings, hepatitis B immune globulin at birth for babies born to mothers who are HBsAg-positive, two-dose hepatitis B vaccine for adults, education and awareness of accessible resources for reducing transmission), migrants from Vietnam where there is a heavy reliance on infant vaccination as the main prevention strategy could be at higher risk due to lack of awareness of disease transmission and prevention strategies. (20) There could also be a lack of health literacy or access to care due to financial, linguistic, and cultural barriers (e.g. stigma, feelings of shame and guilt), which have been documented as contributing factors to health disparities among Vietnamese Americans and Asian American immigrants generally. (21-24) More culturally-tailored public health programs and interventions that aim to increase hepatitis B awareness and knowledge, particularly among Vietnamese Americans born outside of the U.S., are needed.

We identified family history as a significant predictor of hepatitis B risk, which is in line with other screening studies conducted in Vietnamese Americans and Asian Americans. (12, 18, 19) The substantial increased risk among those with a family history is not surprising given that hepatitis B is often transmitted from an infected mother to her baby during birth or through direct contact with blood, semen, or other bodily fluids from an infected person. We also identified gender as a significant predictor with females having a lower risk of hepatitis B than males, which may be a result of biological factors and gender-specific health behaviors and perceptions. Biologically, the observed sex disparity could be due to differences in immune responses which are shaped by sex steroid hormones (e.g. androgens, estrogens) that have been shown to influence the function of immune cells and interact with the complex clinical course of hepatitis B. (25, 26) Behaviorally, females are generally more health conscious and hence may have higher levels of hepatitis B awareness and knowledge as well as greater use of hepatitis B-related prevention services. (27, 28) Males also tend to possess certain lifestyle factors that promote the adoption of more traditional masculine perspectives that underplay the importance of health-protective behaviors. (29, 30) For example, a Vietnamese American male who constructs masculinity as self-reliance or putting work ahead of all other responsibilities may not make time for self-care or seek routine health services, indicating a need to improve health education and outreach for males.

The strengths of our analysis include its large sample size as well as our primary focus on Vietnamese Americans, a community disproportionately burdened by hepatitis B. With the growing literature highlighting the need to disaggregate Asian Americans in research due to the diverse cultures, languages, and sociodemographic factors that characterize each Asian subgroup, it is important that ethnic-specific data are used so more effective public health

strategies can be developed. (31) Our study also used serological tests for HBsAg, anti-HBc, and anti-HBs to accurately classify each participant's hepatitis B status. Many screening fairs have relied solely on HBsAg testing despite the need for anti-HBs and anti-HBc tests to properly identify those truly at risk. We recognize that our findings may not necessarily be generalizable to the entire Vietnamese American population given that attendees of health fairs that offer free services are often foreign-born and from low-income backgrounds. This is indeed true in our analysis since the majority of participants were foreign-born with an annual household income of less than \$30,000 in comparison to only 64% of Vietnamese in the U.S. who are foreign-born with a median annual household income of \$58,700 according to data from the 2013-2015 American Community Survey (ACS). (15) However, there is some comparability with regard to education and marital status when the ACS data are restricted to only those foreign-born (e.g. percent who have a high school education or less: 53% in our data versus 52% in the ACS, percent who are married: 61% in our data versus 64% in the ACS). (15) In addition, Southern California has the highest concentration of Vietnamese Americans in the U.S., making it the ideal region to study hepatitis B for this ethnicity.

Other limitations of our analysis include the lack of information on other factors that may affect hepatitis B risk as well as missing participant data for certain characteristics. These are often issues with questionnaires administered at screening fairs due to time constraints. We did conduct sensitivity analyses with and without the missing data and the overall results did not change. Lastly, our questionnaire data were based on self-report, which may result in misclassification as we noted for participants' hepatitis B vaccination status. However, there is little reason to believe that the misclassification would occur more or less often for those of a certain hepatitis B status, hence any bias would only be towards the null.

Overall, our study provides an updated evaluation on hepatitis B prevalence in the Vietnamese American community and identifies certain subgroups within it, particularly those born outside of the U.S. and those with a hepatitis B family history, who may be at increased risk and require targeted interventions. In addition, we observed important discrepancies between self-reported hepatitis B vaccination status and confirmed serological results, which highlight the need to improve hepatitis B vaccination knowledge among Vietnamese Americans and their health providers. Our comprehensive serological testing makes this a unique effort with findings that can inform strategies to address hepatitis B’s burden in the Vietnamese American community.

TABLE 1. Percentage of screening participants by hepatitis B status

Serological Results	Interpretation	Number of Participants	Percent of Participants*
HBsAg- anti-HBs+/- anti-HBc+	Past infection	1,151	45.9%
HBsAg- anti-HBs+ anti-HBc-	Immunity from vaccination	689	27.5%
HBsAg- anti-HBs- anti-HBc-	Susceptible	443	17.7%
HBsAg+ anti-HBs+/- anti-HBc+	Currently infected	225	9.0%

Note: HBsAg = hepatitis B surface antigen; anti-HBs = hepatitis B surface antibody; anti-HBc = total hepatitis B core antibody

* Does not total 100% due to rounding.

TABLE 2. Characteristics of screening participants by hepatitis B status

Characteristic	Past Infection N (% past infection)*	Immunity from Vaccination N (% vaccinated)*	Susceptible N (% susceptible)*	Currently Infected N (% infected)*	Total	P-value†	P-value**
Gender							
Male	540 (46.9)	276 (40.1)	176 (39.7)	116 (51.6)	1,108	0.02	0.006
Female	609 (52.9)	408 (59.2)	265 (59.8)	108 (48.4)	1,390		
Missing	2 (0.2)	5 (0.7)	2 (0.5)	0 (0.0)	9		
Age							
<40 years	103 (8.9)	208 (30.2)	125 (28.2)	45 (20.0)	481	<0.0001	0.09
40-49 years	232 (20.2)	143 (20.8)	108 (24.4)	62 (27.6)	545		
50-59 years	384 (33.4)	167 (24.2)	114 (25.7)	68 (30.2)	733		
60-69 years	304 (26.4)	120 (17.4)	63 (14.2)	39 (17.3)	526		
70+ years	126 (11.0)	50 (7.3)	33 (7.5)	11 (4.9)	220		
Missing	2 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	3		
Annual Household Income							
≤\$10,000	363 (31.5)	208 (30.2)	137 (29.9)	65 (28.9)	773	0.066	0.021
\$10,001 to \$30,000	405 (35.2)	223 (32.4)	130 (29.4)	91 (40.4)	849		
\$30,001+	185 (16.1)	115 (16.7)	92 (20.8)	32 (14.2)	424		
Missing	198 (17.2)	143 (20.8)	84 (19.0)	37 (16.4)	462		
Education							
Less than high school	260 (22.6)	104 (15.1)	87 (19.6)	39 (17.3)	490	0.004	0.24
High school graduate	394 (34.2)	225 (32.7)	136 (30.7)	87 (38.7)	842		
Some college or technical/vocational training	190 (16.5)	128 (18.6)	77 (17.4)	40 (17.8)	435		
College graduate	223 (19.4)	178 (25.8)	113 (25.5)	44 (19.6)	558		
Missing	84 (7.3)	54 (7.8)	30 (6.8)	15 (6.7)	181		
Marital Status							
Single	290 (25.2)	264 (38.3)	147 (33.2)	63 (28.0)	764	<0.0001	0.31
Married	794 (69.0)	387 (56.2)	279 (63.0)	150 (66.7)	1,610		
Missing	67 (5.8)	38 (5.5)	17 (3.8)	12 (5.3)	134		

Health Insurance							
No	331 (28.8)	190 (27.6)	137 (30.9)	85 (37.8)	744 (29.6)	0.075	0.20
Yes	718 (62.4)	428 (62.1)	260 (58.7)	118 (52.4)	1,534 (60.4)		
Missing	102 (8.9)	71 (10.3)	46 (10.4)	22 (9.8)	244 (9.6)		
Born Outside of the U.S.							
No	7 (0.6)	31 (4.5)	19 (4.3)	1 (0.4)	58 (2.3)	<0.0001	0.006
Yes	1130 (98.2)	644 (93.5)	415 (93.7)	223 (99.1)	2,413 (97.7)		
Missing	14 (1.2)	14 (0.6)	9 (2.0)	1 (0.4)	38 (1.5)		
Family History of Hepatitis B							
No	707 (61.4)	395 (57.3)	281 (63.4)	118 (52.4)	1,503 (59.3)	0.0001	<0.0001
Yes	116 (10.1)	69 (10.0)	37 (8.4)	44 (19.6)	266 (10.5)		
Missing	328 (28.5)	225 (32.7)	125 (28.2)	63 (28.0)	744 (29.2)		
Previous Hepatitis B Vaccination							
No	662 (57.5)	263 (38.2)	245 (55.4)	150 (66.7)	1,320 (51.6)	<0.0001	0.017
Yes	203 (17.6)	225 (32.7)	71 (16.0)	25 (11.1)	524 (20.5)		
Missing	286 (24.9)	201 (29.2)	127 (28.7)	50 (22.2)	666 (26.1)		
Total:	1,151	689	443	225	2,508		

* May not total 100% due to rounding.

† Number of participants by each characteristic.

‡ Chi-square p-value comparing all four hepatitis B statuses.

** Chi-square p-value comparing only those susceptible to hepatitis B to those currently infected with hepatitis B.

TABLE 3. Odds ratio and 95% confidence intervals for the association between screening participant characteristics and risk of hepatitis B

Characteristic	Odds Ratio*	95% Confidence Interval	P-value
Gender			
Male	1.00	--	--
Female	0.48	0.33 – 0.69	<0.0001
Age			
<40 years	1.00	--	--
40-49 years	1.40	0.83 – 2.36	0.20
50-59 years	1.58	0.95 – 2.62	0.078
60-69 years	1.54	0.85 – 2.79	0.15
70+ years	0.76	0.32 – 1.77	0.52
Annual Household Income			
≤\$10,000	1.00	--	--
\$10,001 to \$30,000	1.32	0.86 – 2.03	0.35
\$30,001+	0.56	0.32 – 0.99	0.046
Born Outside of the U.S.			
No	1.00	--	--
Yes	13.36	1.62 – 110.05	0.016
Family History of Hepatitis B			
No	1.00	--	--
Yes	4.68	2.66 – 8.22	<0.0001
Previous Hepatitis B Vaccination			
No	1.00	--	--
Yes	0.53	0.31 – 0.93	0.023

* Adjusted for all other characteristics as well as year of screening.

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CONTRIBUTORS

AWL, WJ, BN, and TVN contributed to the conception and design of the study. BN, DNH, JNH, and TVN contributed to the study's data collection. AWL, WJ, EC, and PY contributed to statistical analysis and interpretation of the data. AWL, WJ, and EC drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

ETHICS APPROVAL

All data analyzed in this report had institutional ethics committee approval from California State University, Fullerton (research project number: HSR-17-18-515).

DATA SHARING STATEMENT

No additional data available.

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COMPETING INTERESTS

The authors have no competing interests to disclose.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cross-sectional studies

****NOTE: All page numbers reported here are based on the clean version of the revised manuscript****

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what is sound	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8-9
		(b) Describe any methods used to examine subgroups and interactions	8-9
		(c) Explain how missing data were addressed	8-9
		(d) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	8-9

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 9
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10, 17-18
		(b) Indicate number of participants with missing data for each variable of interest	17-18
Outcome data	15*	Report numbers of outcome events or summary measures	9, 16-18
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 19
		(b) Report category boundaries when continuous variables were categorized	8, 17-18
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.