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Review

Lower vaccine uptake amongst older individuals living alone: A systematic review and meta-analysis of social determinants of vaccine uptake

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ABSTRACT

Introduction: Vaccination is a key intervention to reduce infectious disease mortality and morbidity amongst older individuals. Identifying social factors for vaccine uptake enables targeted interventions to reduce health inequalities.

Objective: To systematically appraise and quantify social factors associated with vaccine uptake amongst individuals aged ≥60 years from Europe.

Methods: We searched Medline and Embase from inception to 24/02/2016. The association of vaccine uptake was examined for social factors relevant at an individual level, to provide insight into individuals' environment and enable development of targeted interventions by healthcare providers to deliver equitable healthcare. Factors included: living alone, marital status, education, income, vaccination costs, area-level deprivation, social class, urban versus rural residence, immigration status and religion. Between-study heterogeneity for each factor was identified using I^2-statistics and Q-statistics, and investigated by stratification and meta-regression analysis. Meta-analysis was conducted, when appropriate, using fixed- or random-effects models.

Results: From 11,754 titles, 35 eligible studies were identified (uptake of: seasonal influenza vaccine (SIV) only (n = 27) or including pneumococcal vaccine (PV) (n = 5); herpes zoster vaccine (n = 1); pandemic influenza vaccine (n = 1); PV only (n = 1)). Higher SIV uptake was reported for individuals not living alone (summary odds ratios (OR) = 1.39 (95% confidence interval (CI): 1.16–1.68). Lower SIV uptake was observed in immigrants and in more deprived areas: summary OR = 0.57 (95%CI: 0.47–0.68) and risk ratio = 0.93 (95%CI: 0.92–0.94) respectively. Higher SIV uptake was associated with higher income (OR = 1.26 (95%CI: 1.08–1.47)) and higher education (OR = 1.05 (95%CI: 1–1.11)) in adequately adjusted studies. Between-study heterogeneity did not appear to result from variation in categorisation of social factors, but for education was partly explained by varying vaccination costs (meta-regression analysis p = <0.0001); individuals with higher education had higher vaccine uptake in countries without free vaccination.

Conclusions: Quantification of associations between social factors and lower vaccine uptake, and notably living alone (an overlooked factor in vaccination programmes), should enable health professionals target specific social groups to tackle vaccine-related inequalities.

Contents

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1. Introduction

Vaccination is an important intervention to prevent infections amongst older individuals, who have increased susceptibility to infections and often experience more severe outcomes [1–3]. A successful vaccination programme depends not only on vaccine effectiveness and well-organized programme delivery but also on high vaccination uptake [3]. Inequalities in vaccine uptake amongst older individuals could be related to social factors: the social circumstances of living and working [4–6]. Determining the association between social factors and vaccine uptake helps to quantify any vaccination inequalities in specific population groups and assists health care providers in planning targeted interventions and making any necessary changes to vaccination programmes. The social factors affecting vaccine uptake may vary with age and with the type of vaccine [4–7]. A 2011 systematic review summarised the association of social determinants of health with uptake of a single vaccine (seasonal influenza (SIV)) for older individuals (aged ≥65 years), without quantitative synthesis [6]. This previous study found conflicting associations of factors such as education, marital status, ethnicity, socio-economic level and place of residence, without undertaking a comprehensive assessment of between-study heterogeneity [6].

The social factors associated with SIV uptake may be different from other vaccines used for older adults such as pneumococcal and herpes zoster vaccines that are not administered annually. The objective of this review was to systematically appraise and quantify the association of social factors with uptake of vaccines amongst individuals aged ≥60 years from Europe including a detailed between-study heterogeneity assessment when necessary. It was anticipated that the studies from the European region may be more homogenous compared to those from low-income settings, making data synthesis more feasible.

2. Methods

2.1. Search strategy

This review formed part of a larger search for studies exploring social determinants of vaccine uptake in Europe for all age groups. The wider search ensured that studies spanning different age groups, including subgroups of older individuals, were not potentially missed. The data sources comprised Medline and Embase, searched from inception to 24/02/2016. Search terms (text words and subject headings) were drawn up for four search concepts: social factors, the European region [8], vaccination and uptake. The search included articles, letters and conference abstracts published in English. Additionally, reviews of vaccine uptake (worldwide from the last five years) were searched to identify further European studies. The detailed search strategy is provided in Appendix-1. Reference lists of all eligible studies and reviews were also searched.

To identify social factors associated with vaccine uptake, we adapted the conceptual framework developed by the World Health Organisation's Commission on Social Determinants of Health (Appendix-2) [7] for tackling health inequalities globally. This framework provides a comprehensive approach for identifying complex relationships between social factors and inequality, and how to plan and implement interventions. We sought evidence for social factors relevant at an individual level or provided insight into individuals' environment that could assist healthcare providers to target specific social groups for equitable healthcare delivery. The following factors were identified as possible determinants of vaccine uptake: country of birth, religion, urban/rural residence, marital status, living arrangements (living with others versus living alone), and socio-economic position (education, income (individual or household), type of health insurance, area-level socio-economic status (SES), social class/occupation). For the purposes of this review, we did not examine factors that were possible mediators of the main factors of interest: knowledge, attitude and beliefs, access to healthcare and health status/co-morbidities (Appendix-2).

The titles and abstracts of the records retrieved were screened for full text assessment based on *a priori* inclusion criteria (Appendix 3). Studies reporting the effect of one or more social factor of interest on vaccine uptake amongst individuals aged ≥60 years from Europe [8] were potentially eligible. The outcome was any routine vaccination programme and/or one-off vaccination such as pandemic mass vaccinations or catch-up vaccinations; travel or occupational health vaccinations were excluded. Eligible study designs comprised cross-sectional, ecological, case-control or cohort studies. We further restricted to studies that quantified the relationship between social factors of interest with vaccine uptake by either reporting relative risks or providing raw data for their calculation; studies presenting the results of hypothesis testing without reporting effect measures were described narratively. Multiple papers describing the same study population were included once. The abstracts of the records that appeared to meet these screening criteria were selected for a full text review.

The eligibility criteria were applied by one reviewer (AJ) to the titles/abstracts identified, for full-text assessment. A random sample (10%) of titles considered ineligible were screened independently by two other reviewers (ST and AJVH) (no disagreements were observed). Of the total records identified for full text review, the eligibility for 10% of the records for which eligibility was initially unclear was resolved by discussion (ST, AJ and AJVH).

2.2. Data extraction

Data were extracted by one reviewer (AJ). Information was extracted for: author, study characteristics (year, country, design, size, participants) vaccine types, social factors, effect estimates and confounders used for adjusted effect estimates.

2.3. Quality assessment

Quality assessment was performed by one reviewer (AJ) including detailed discussions with the second reviewer (ST), using the Cochrane approach for risk of bias adapted for observational data [9,10]. Risk of bias (categorised as low, high or unclear risk) was assessed for the following five domains: selection bias, missing data, misclassification of vaccination status, misclassification of social factors (including consideration of timeliness for time-varying social factors - marital status, living alone, rural/urban residence, area-level SES, income and insurance status), and confounding bias. Details of the bias assessment are provided in the Appendix-4.

2.4. Data analysis

Forest plots of effect estimates (odds ratios (OR) or risk/rate ratios (RR)) were generated for each social factor, stratified by vaccine type. Raw data were used to calculate ORs if effect estimates were unavailable. The effect estimates from the most appropriate model (ideally, controlling for confounding and not adjusted for mediating variables) were used when available, otherwise the unadjusted estimate was used. For social factors with more than two categories, reported estimates for the highest or lowest category were selected. To address varying choice of baseline exposure group in different studies, effect estimates for a comparable baseline were re-calculated when possible using raw data; if the exposure variable was binary, the effect estimates were reversed for studies that used a different baseline. Similarly, effect estimates for non-uptake of vaccination were reversed to obtain estimates for vaccine uptake. Studies were described narratively if such comparisons were impossible or if estimates from probit or linear probability models were presented.

Between-study heterogeneity was explored using I^2-statistics and the Cochrane Q-statistic [11]. When the I^2-statistic was $\leq$50% fixed effects meta-analyses [11] were conducted. When between-study heterogeneity ($I^2 > 50\%$) was identified for a particular factor, a random effects meta-analysis was conducted if effect estimates were all broadly in the same direction, but was not attempted when effect estimates were in opposing directions as the summary estimate was considered uninformative [11].

Between-study heterogeneity was explored as follows: stratifying by vaccine type (influenza vs other vaccine uptake), different effect measures (OR or RR), re-categorising exposures with >2 categories (when feasible) to maximise homogeneity of exposure definitions; restricting analyses to studies reporting adequately adjusted estimates (Appendix 4), and stratifying results by whether the vaccine was available free-of-charge in the country (to see whether costs of vaccination modified effect estimates).

Meta-regression analysis was conducted to further investigate heterogeneity for social factors with at least 10 studies, assessing: vaccine type (influenza vs other vaccine uptake); OR/RR as effect estimates; heterogeneity in the categories chosen for the social factor; confounding bias; whether the vaccine was available free-of-charge; and any over-adjustment of effect estimates (inclusion of hypothesized mediating variables in multivariable models).

Data were analysed using Stata 14 software package (StataCorp LP, College Station, TX, USA).

3. Results

A total of 11,754 titles were identified, of which 479 titles (including one title identified from references) were evaluated for full text review (Appendix-5) resulting in 35 eligible studies conducted between 1997 and 2015 (Appendix-6). Most were cross-sectional with five cohort studies and one case-control study. Three studies reported data for more than one European country [12–14], with the remaining 32 studies conducted in 11 countries (Table 1), Spain being the most frequent (n = 11) followed by the UK (n = 5). The studies ascertained uptake of SIV (n = 27), pneumococcal vaccine (PV) (n = 1), both SIV and PV (n = 5), SIV and pandemic influenza vaccine (n = 1), and SIV and herpes zoster vaccine (n = 1).

Amongst studies providing effect estimates education was the most frequent social factor investigated (n = 14), followed by living alone (n = 13), and country of birth (n = 11). The least studied factors were health insurance (n = 3) and religion (n = 1) (Table 1). Two studies reported effect estimates for some social factors but only statistical evidence (without effect estimates) for country of birth [15] and for private medical insurance [16] (Appendix-7). Nine additional studies [17–25] (Appendix-7) that did not provide effect estimates were summarised narratively.

3.1. Quality assessment

As shown in Table 2 and Appendix-8, studies had low risk of bias for outcome and exposure measurement but confounding bias was common. The confounding bias mostly resulted from lack of adjustment for at least one other social factor (Appendix-4) in multivariable models.

3.2. Social factors of vaccine uptake

3.2.1. Living alone

Of the nine studies considered for meta-analysis, six classified living alone as a binary variable, and for the other three [26–28] studies "living as a couple" was compared to living alone. Although results were heterogeneous, studies consistently showed increased uptake amongst those not living alone, with an overall 25% and 53% increase for SIV uptake after restricting analysis to adequately adjusted studies and stratifying by vaccine cost respectively (Fig. 1). Re-analysis of living arrangements as a binary variable (Fig. 1) did not reduce heterogeneity.

Two studies [29,30] categorised living arrangements differently. One (comparing smaller versus larger households) reported increased uptake amongst individuals from large households [29], whereas the other (living with children versus not living with children) [30] reported lower vaccine uptake amongst those living with children. The studies that used probit or linear regression models found negative associations between vaccine uptake and housing density [31] and those living with children [14]. The single

Table 1
Summary of studies reporting associations of social determinants with vaccine uptake (N = 35).

	First author	Country	Study period	Sample size	Study population	Vaccine	Social determinants and their association with vaccine uptake									
							SES (A)[a]	Inco[b]	SC[c]	COB[d]	Edu[e]	LA[f]	RS[g]	Reli[h]	Res[i]	HI[j]
Cross-sectional studies																
1	Abramson [32]	Israel	1997	626	People aged ≥65 years with a telephone and registered at the Jerusalem community centre	SIV				$N^{*\delta}$	N^*		$\downarrow^*$	N^*		
2	Aguilar [56]	Spain	2010–2011	104,427	Computerised vaccination records for all non-institutionalised individuals ≥65 years covered by Navarre Health Service	SIV				$\downarrow^*$					N^*	
3	Barrett & Mc Hugh [33,47]	RoI	October 2009–February 2011	3,510	Community residents aged ≥65 years from The Irish Longitudinal Study on Ageing (TILDA)	SIV		$\downarrow$			$\downarrow$					$\uparrow$
4	Bodekar [15]	Germany	March–June 2014	825	Respondents (aged ≥60 years) to a nationwide telephone survey	SIV					N					
5	Bohmer [37]	Germany	July 2008–June 2009	8,458	Respondents (aged ≥60 years) to a national telephone health survey	SIV		N^*			N					
6	Burns [57]	UK	2001–2002	444	Adults aged ≥65 years interviewed at public places around Birmingham	SIV			$\downarrow^*$			$\uparrow^*$				
7	Carreno-Ibanez [58]	Spain	March–June 2014	76,782	Individual records from the primary care electronic records for people aged ≥60 years with chronic bronchitis or emphysema from the Autonomous Community of Madrid	PV				$\downarrow$						
8	Chiatti [26,48,59]	Italy	December 2004–September 2005	25,183 (3,738 with COPD)	People (aged ≥65 years) from the "Healthstatus of the population and use of health services in Italy" survey (ISTAT 8) and a secondary analysis of individuals who self-reported a diagnosis of COPD	SIV		N^*	$\uparrow^*$		N^*	N^*	$\downarrow^*$			
9	Christenson [34]	Sweden	December 2000–May 2001	7,631	Responders (aged ≥65 years) of a postal survey sent to people registered with the Stockholm County Council Population Register	SIV & PV					$\uparrow$		$\downarrow$			
10	Crawford [12]	UK and RoI	2004	2,033	Community residents (aged ≥65 years) surveyed as a part of "Healthy Aging Research Programme"	SIV			N^*			N^*	N^*		N^*	
11	Damiani [35]	Italy	September 1999–June 2000	24,564	Respondents (aged 65–89 years) to the Italian national survey	SIV		$\uparrow^*$	N^*		N^*		$\downarrow^*$			
12	de Souto [42]	France	May–July 2011	6,275	Residents from 175 nursing homes in the Midi-Pyrenees region	SIV & PV									SIV: N^*; PV $\downarrow^*$	
13	Jimenez-Garcia [60]	Spain	2003	6,134	Non-institutionalised participants (aged ≥65 years) in the Spanish National Health survey	SIV				N^*						
14	Jimenez-Garcia [61]	Spain	June 2006–June 2007	7,835	Non-institutionalised respondents (aged ≥65 years) to the Spanish National Health survey	SIV				$\downarrow^*$						
15	Jimenez-Garcia [62]	Spain	November 2004–June 2005	1,629	Respondents (aged ≥65 years) to the "Madrid City Health Survey: ESCM 05″	SIV				N^*						
16	Jimenez-Garcia [63]	Spain	July 2011–June 2012	5,725	Non-institutionalised respondents (aged ≥60 years) to the Spanish National Health Survey	SIV				$\downarrow^*$						
17	Jimenez-Garcia [64]	Spain	2012–2013	1,307,165	Records of people aged ≥60 years registered with the public health system of the Autonomous Community of Madrid	SIV				$\downarrow^*$						
18	Kroneman [29]	Sweden	April–May 2004 & March–April 2005	612	Respondents (aged ≥65 years) to a national telephone survey	SIV						N^*				
19	Landi [13]	11 countries^	2001–2003	3,878	Participants from urban areas aged ≥65 years from 11 European countries that took part in the "Aged in Home Care (ADHOC) project" of EU	SIV		$\uparrow^*$				$\uparrow^*$				
20	Mamelund [36]	Norway	November 2008	354	Non-institutionalised participants aged ≥65 years of a national telephone survey	SIV		N			N	N				
21	Nexoe [65]	Denmark	September 1996 & February 1997	1,204	Respondents to postal questionnaires aged ≥65 years identified from the Civil Registration System	SIV						$\uparrow^*$				
22	Opstelten [45]	Netherlands	1999	666	Respondents to a postal questionnaire, aged ≥65 years and registered with 4 general practices in Amersfoort town	SIV and PV										$\downarrow^*$
23	Opstelten [49]	Netherlands	September 2007	1,221	Respondents to postal questionnaire, aged ≥65 years and registered with 3 general practices in Amersfoort town	HZ & SIV					$\downarrow^*$					
24	Pena-Rey [50]	Spain	January 2000	1,111	Participants (aged ≥65 years) in a women's social and health	SIV		$\uparrow^*$			N		$\downarrow^*$		N^*	

Table 1 (*continued*)

	First author	Country	Study period	Sample size	Study population	Vaccine	Social determinants and their association with vaccine uptake									
							SES (A)[a]	Inco[b]	SC[c]	COB[d]	Edu[e]	LA[f]	RS[g]	Reli[h]	Res[i]	HI[j]
					survey in Galicia											
25	Sarria-Santamera [16]	Spain	1997	1,148	Non-institutionalised participants (aged ≥65 years) in the Spanish National Health survey (ENS)	SIV		N			N					
26	Schmitz [14]	15 countries	2004 & 2006	8,891	Respondents aged ≥65 years from the first and the second wave of the Survey of Health, Ageing and Retirement in Europe (SHARE)	SIV					$\uparrow^{*\alpha}$	$\downarrow^{*\alpha\zeta}$	$\uparrow^{*\alpha\tau}$			
27	Shahrabani [31]	Israel	1999–2000	4,083	Respondents (aged ≥60 years) to the Health Survey of the Central Bureau of Statistics	SIV				$\downarrow^{*\alpha\varepsilon}$	$N^{*\alpha}$	$\downarrow^{*\alpha\eta}$	$\downarrow^{*\alpha}$			
28	Sintes [28]	Spain	May 2005–January 2007	1,702	Non-institutionalised patients aged ≥65 years admitted with community acquired pneumonia to 3 acute general hospitals in Catalonia and Galicia	SIV & PV			SIV: N, PV: ↑		SIV: N, PV:↓	$\uparrow^{*}$			N	
29	Wershof Schwartz [43]	Israel	2008–2009	136,944	Individuals aged ≥65 years and registered with Maccabi Healthcare Services	SIV & PV	$\downarrow^{*}$			$\downarrow^{*}$					$\uparrow^{*}$	
Casecontrol study																
30	Van Essen [46]	TN	1993–1994	181	Respondents (aged ≥65 years) to a postal questionnaire, registered with seven family practices situated in a suburban area	SIV						N^{*}				N^{*}
Cohort studies																
31	Breeze [41]	UK	1997–2000	29,731	People aged >74 years with available flu vaccination records registered with general practices in the UK taking part in the “Trial of Assessment and Management of Older People in the Community Study”	SIV	N^{*}	N^{*}							N^{*}	
32	Mangtani [27]	UK	2000	5,572	People aged >74 years from the “Trial of Assessment and Management of Older People in the Community”	SIV	N^{*}	N^{*}				↑	↓		$\uparrow^{*}$	
33	Martinez-Baz [30]	Spain	2010–2011	64,245	Individual records of non-institutionalised people aged ≥65 years and previously vaccinated in 2009–2010 Navarre	SIV				$\downarrow^{*}$		$\downarrow^{*\theta}$			N^{*}	
34	Sammon [44]	UK	August 2009–June 2010	353,921	Individuals aged ≥65 years in clinical risk groups and registered with a practice contributing to the General Practice Research Database at the beginning of the H1N1 vaccination campaign	SIV & PIV	SIV: $N^{*\beta}$; PIV:$\downarrow^{*\beta}$									
35	Shah [66]	UK	June 2008–January 2009	387,568	Individual records of community and care (nursing and residential) home residents aged 65–104 years and registered with a practice contributing to The Health Improvement Network primary care database	SIV	$\downarrow^{*}$									
	Total number of studies (%)						5 (14%)	10 (29%)	5 (14%)	11 (31%)	14 (40%)	13 (37%)	9 (26%	1 (3%)	9 (26%)	3 (9%)

SES(A) – socio-economic status area [a] most deprived versus least deprived (reference group) except for [β]Sammon et al. (3rd quintile: reference group).
Inco – income [b] Highest income level versus lowest income level (reference group).
SC – social class [c] Lowest social class versus highest social class (reference group).
COB – country of birth [d] Immigrants versus native (reference group) ([δ]Abramson et al.: others versus those from Asia/Africa (reference group), [α]probit marginal probabilities [ε]Shahrabani et al. individuals from USSR (after 1990) versus native (reference group)).
Edu – education [e] Highest education level versus lowest education level (reference group).
LA – living arrangements [f] Not living alone versus living alone/smaller household size (reference group); [ζ]Schmitz et al. number of children in household (ordinal variable); [η]Shahrabani et al. housing density (ordinal variable); [θ]Martinez-Baz et al. living with children aged <15 years versus not living with children aged <15 years (reference group).
RS – relationship status [g] Not married versus married (reference group); [τ]Schmitz et al. no partner (reference group).
Reli – Religion [h] Not religious versus religious (reference group).
Res – Residence [i] Urban versus rural area (reference group).
HI – health insurance [j] Private insurance versus no private insurance (reference group).
SIV seasonal influenza vaccine PIV pandemic influenza vaccine PV pneumococcal vaccine HZ herpes zoster vaccine.
N – not associated with vaccine uptake. *adjusted estimates ↓ lower vaccine uptake ↑ higher vaccine uptake.
RoI – Republic of Ireland, COPD – Chronic Obstructive Pulmonary Disease.
^11 countries Czech Republic, Denmark, Finland, France, Germany, Iceland, Italy, The Netherlands, Norway, Sweden, UK.
~15 countries Austria, Belgium, Czech Republic , Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Poland, Spain, Sweden, Switzerland & Israel.

Table 2
Quality assessment of the studies included in the review.

Study type & Ref.	Social determinants and bias																																		
			Area SES			Income			Social class			COB			Education			Living alone			Marital status			Religion			Residence			Insurance		
Cross-sectional	SB	OM	EM	CB	MD	EM	CB	MD	EM	CB	MD	EM	CB	MD	EM	CB	MD	EM	CB	MD	EM	CB	MD	EM	CB	MD	EM	CB	MD	EM	CB	MD
[32]	L	L										L	L	U	L	L	U				L	L	U	L	L	U						
[56]	L	L										L	L	L													U	L	L			
[33, 47]	H	L				H	H	H							L	H	L													H	H	L
[15]	H	L													L	H	L															
[37]	H	L				L	L	U							L	H	U															
[57]	L	L							L	L	L							L	L	L												
[58]	L	L										L	H	L																		
[26, 48, 59]	U	L				L	L	L	L	L	L				L	L	L	L	L	L	L	L	L									
[34]	L	L													L	H	L				L	H	L									
[12]	H	L							L	L	U							L	L	U	L	L	U				L	L	U			
[35]	U	L				L	L	L	L	L	L				L	L	L				L	L	L									
[42]	H	L																									L	L	L			
[60]	U	L										L	H	L																		
[61]	U	L										L	H	L																		
[62]	U	L										L	H	U																		
[63]	U	L										L	H	L																		
[64]	L	L										L	H	L																		
[29]	U	L																L	H	U												
[13]	U	L				L	L	L										L	L	L												
[36]	H	L				L	H	H							L	H	L	L	H	L												
[65]	H	L																L	H	L												
[45]	H	L																												L	H	L
[49]	H	L													L	H	L															
[50]	L	L				L	L	L							L	H	L				L	L	L				L	L	L			
[16]	L	L				L	H	L							L	H	L															
[14]	U	L													L	L	U	L	L	U	L	L	U									
[31]	U	L										L	L	U	L	L	U	L	L	U	L	L	U									
[28]	U	L							L	H	L				L	H	L	L	H L*	L							L	H	L			
[43]	L	L	H	L	L							L	L	L													L	L	L			
Cohort																																
[41]	U	L	L	L	L	L	L	L																			L	L	L			
[27]	L	L	L	L	L	L	L	L										L	H	L	L	H	L				L	L	L			
[30]	U	L										L	L	U				U	L	U							U	L	U			
[44]	U	L	U	H	U																											
[66]	U	L	U	H	L																											
Case-control																																
[46]	L	L																L	L	L										L	L	L

Ref. – reference, SES – socioeconomic status, COB – country of birth, SB – selection bias, OM – outcome misclassification, EM – exposure misclassification, CB – confounding bias, MD – missing data, L – low risk of bias, U – unclear risk of bias, H – high risk of bias.
Red cell with letter H signifies high risk of bias.
Green cell with letter L signifies low risk of bias.
Yellow cell with letter U signifies unclear risk.
*Low risk of bias for pneumococcal vaccine.

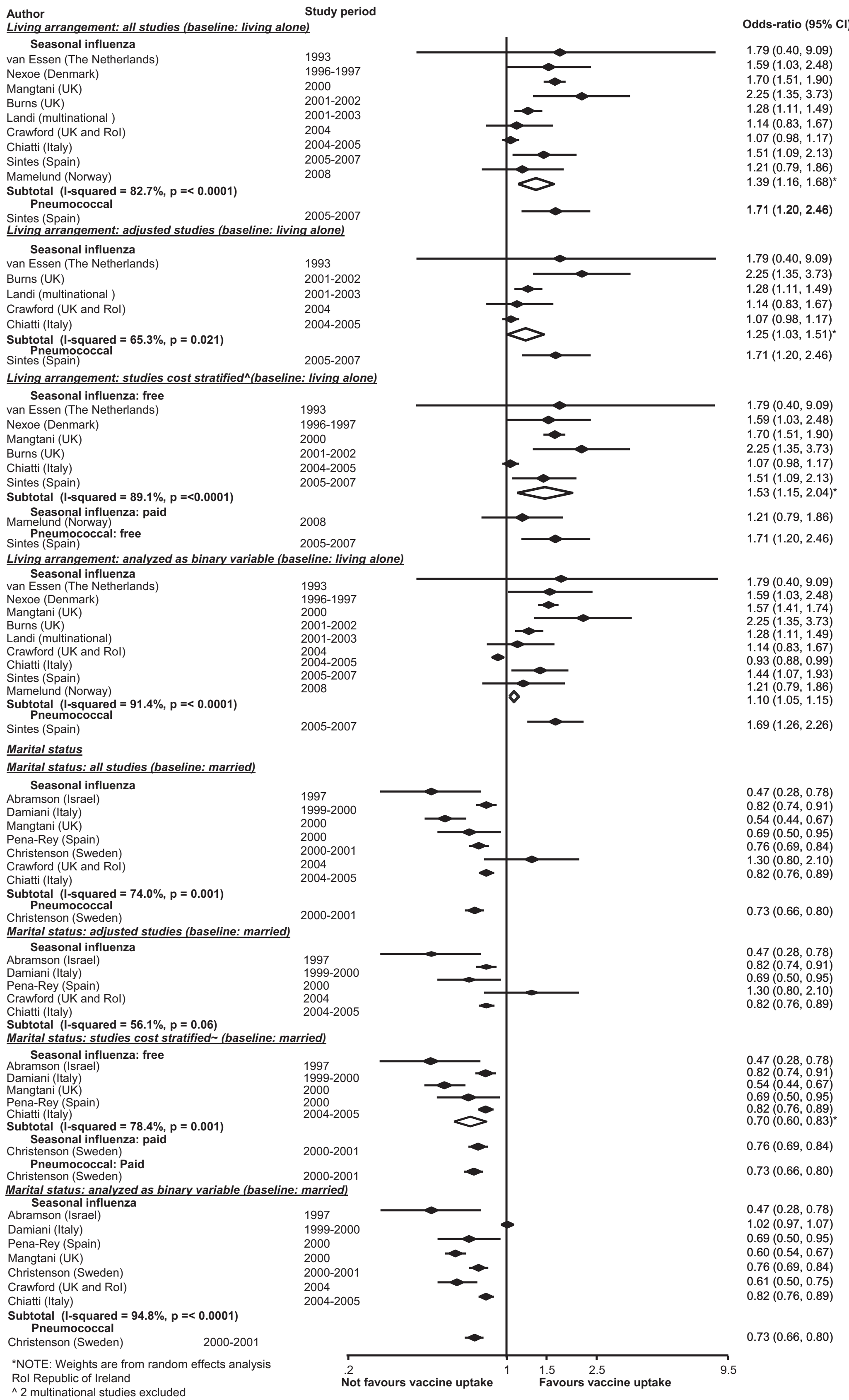


Fig. 1. Effect of living arrangements and marital status on vaccine uptake.

UK study that did not provide effect measures, found no association between living arrangements (categorised as a seven-level variable) and SIV uptake amongst patients admitted to a geriatric ward [20] (Appendix-7).

3.2.2 Marital status

Four of the seven studies considered in the meta-analysis categorised marital status as a binary variable, for the remaining three studies single status was compared to being married. After stratification by vaccine type, 18–53% lower vaccine uptake was observed amongst unmarried individuals in all studies except one [12] with notable between-study heterogeneity (I^2 = 74%, Fig. 1). Reclassifying marital status in three studies as a binary variable (unmarried versus married) did not reduce the between-study heterogeneity (Fig. 1). Heterogeneity was reduced but still appreciable after restricting analyses to adequately adjusted SIV uptake studies. Results were more homogeneous after stratifying by vaccine cost; in countries in which SIV was free-of-charge, overall uptake amongst unmarried individuals was 30% lower compared to married individuals (Fig. 1), echoing findings for living arrangements (Fig. 1). The studies that used linear probability [14] or probit models [31] also found higher SIV uptake amongst married individuals or those with a partner, as did one of the three Spanish studies that did not provide effect measures (uptake 47.8% vs 53%) [21]; the other two Spanish studies found no evidence for an association between marital status and SIV uptake [16,18] (Appendix-7).

3.2.3. Education

Twelve studies were considered for meta-analysis (Fig. 2). There was no consistent effect of higher education on vaccine uptake after stratification by vaccine-type (I^2 > 80%). Results were little changed after re-categorising education in seven studies as a binary variable (education up to ages 12–15 years and >15 years) [16,26,32–36] (Fig. 2). Restricting analysis to adequately adjusted studies resulted in a consistent direction of effect (Fig. 2) with a summary estimate of 5% higher uptake amongst those with the highest education level.

Interestingly, stratification by vaccination cost [32,34,35,37–40] showed marked differences. In countries where the vaccine was provided free-of-charge there was no overall effect of education. In contrast, in countries where a payment for vaccination was necessary, higher education was associated with an overall 67% increased odds of SIV uptake. (Fig. 2). A reverse effect (20% decreased odds of uptake) was seen in the single Irish study, where vaccine administration payments are means tested [39,40].

Two studies excluded from meta-analysis reported marginal probabilities: one found no evidence of an association of education level with SIV uptake [31] and the other (including fifteen countries) found low education level associated with lower SIV vaccination (linear probability model coefficient = −0.034) [14]. Four further studies did not provide effect estimates: a Greek study [24] showed higher uptake amongst those with at least primary education whilst three Spanish studies [18,21,22] reported no evidence of effect of education on SIV uptake (Appendix-7).

3.2.4. Household/individual income

The eight studies that reported ORs for income and SIV uptake showed no consistent effect (Fig. 2). Amongst the two studies [27,41] reporting RRs, there was no overall effect of income on SIV uptake (Fig. 2).

Despite remaining heterogeneity, results were more consistent after restricting to studies with adequate adjustment for confounding, with an overall 26% increased odds of SIV uptake amongst those with higher income, consistent with that observed for the effect of education (Fig. 2). Unlike the findings for education, in stratified analyses an overall 14% higher odds of SIV uptake amongst those with higher income was observed in countries offering free-of-charge vaccination [37,40] (Fig. 2). However, in a single Irish study [33] where vaccination payment was means tested [40], the effect of higher income was similar to that of higher education: those with higher income had lower odds of SIV uptake (Fig. 2). It was not possible to re-classify income status as a binary variable for comparison across studies, and the exploration of heterogeneity for this aspect was therefore not undertaken.

Four studies did not provide effect estimates for the association of income with vaccine uptake (Appendix-7). A second Irish study found uptake of both SIV and PV to be higher ($p < 0.001$) amongst individuals entitled to free vaccine (possessors of a medical card) compared to those who paid for vaccination [17]. Higher SIV coverage was reported for individuals with lower income in urban areas of Turkey where the vaccination was not available free-of-charge [19]. In contrast, two Spanish studies found no evidence of an association between income and SIV uptake [18,21].

3.2.5. Urban or rural area of residence

Eight of the nine studies (SIV n = 6, SIV and PV n = 3) with effect estimates reported the association of vaccine uptake with the location of individuals' own homes (urban or rural), whilst one French study [42] investigated the location of individuals' nursing homes (Fig. 3). No consistent direction of effect was observed for studies reporting ORs for the association of SIV uptake with residence. However, the studies that presented RRs for SIV uptake and ORs for PV uptake found an overall 11% and 15% increase in uptake respectively amongst urban residents (Fig. 3).

The location of nursing homes had no effect on SIV uptake, but (in contrast to individuals living independently) a lower uptake of PV was observed in residents in urban versus rural nursing homes (Fig. 3).

Between-study heterogeneity for SIV uptake could not be explained by restricting the analysis to adjusted ORs (Fig. 3) and all studies except one [12] offered free vaccination. Again, it was not feasible to re-categorise this exposure as binary variable.

A UK study that did not provide effect measures found no association between location of general practices and SIV uptake [23].

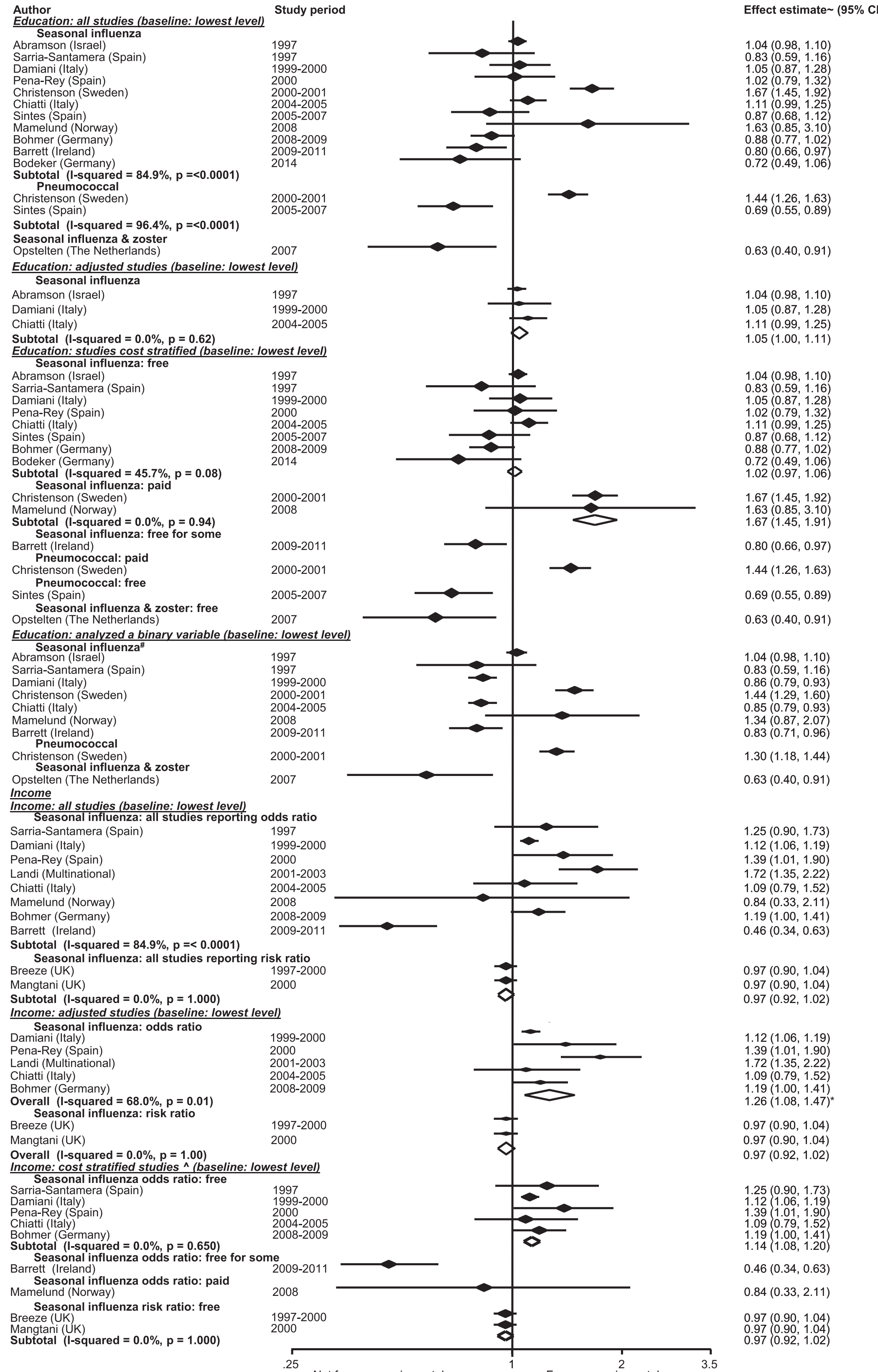
3.2.6. Area-level SES

Five UK studies reported the association of area-level SES with vaccine uptake (SIV alone n = 3, SIV and pandemic influenza n = 1, SIV and PV n = 1, Fig. 3). All but one study reported RRs [43]. The reference group for one study [44] was the third quintile of deprivation in contrast to the other four studies (the baseline group being the least deprived area).

The results were similar to the effect of household income (Fig. 2), with risk of SIV uptake modestly (7–11%) lower amongst those living in most deprived areas. This effect was seen consistently irrespective of vaccine type or measure of effect (Fig. 3) or using a different baseline group. All studies were from countries providing free-of-charge vaccination and it was not feasible to re-categorise this exposure.

3.2.7. Private medical insurance

Two [45,46] of the three studies considered in meta-analysis categorised insurance as a binary variable; one study [47] used a four-level variable (Appendix-6). The latter study compared individuals with private medical insurance to those without insurance as baseline. After stratification by vaccine types (Fig. 3), overall SIV uptake was 67% more likely amongst individuals with private medical insurance, but uptake of both SIV and PV was 62% lower (Fig. 3). One study [46] provided adequately adjusted estimates; all but one study [47] were conducted in countries that provided vaccine free-of-charge (Fig. 3). SIV uptake was 72% higher amongst



~All effect estimates are odds ratio unless specified otherwise
Subtotal (I-squared = 92.7%, p =< 0.0001) *NOTE: Weights are from random effects analysis ^One multinational study excluded

Fig. 2. Effect of education and income on vaccine uptake.

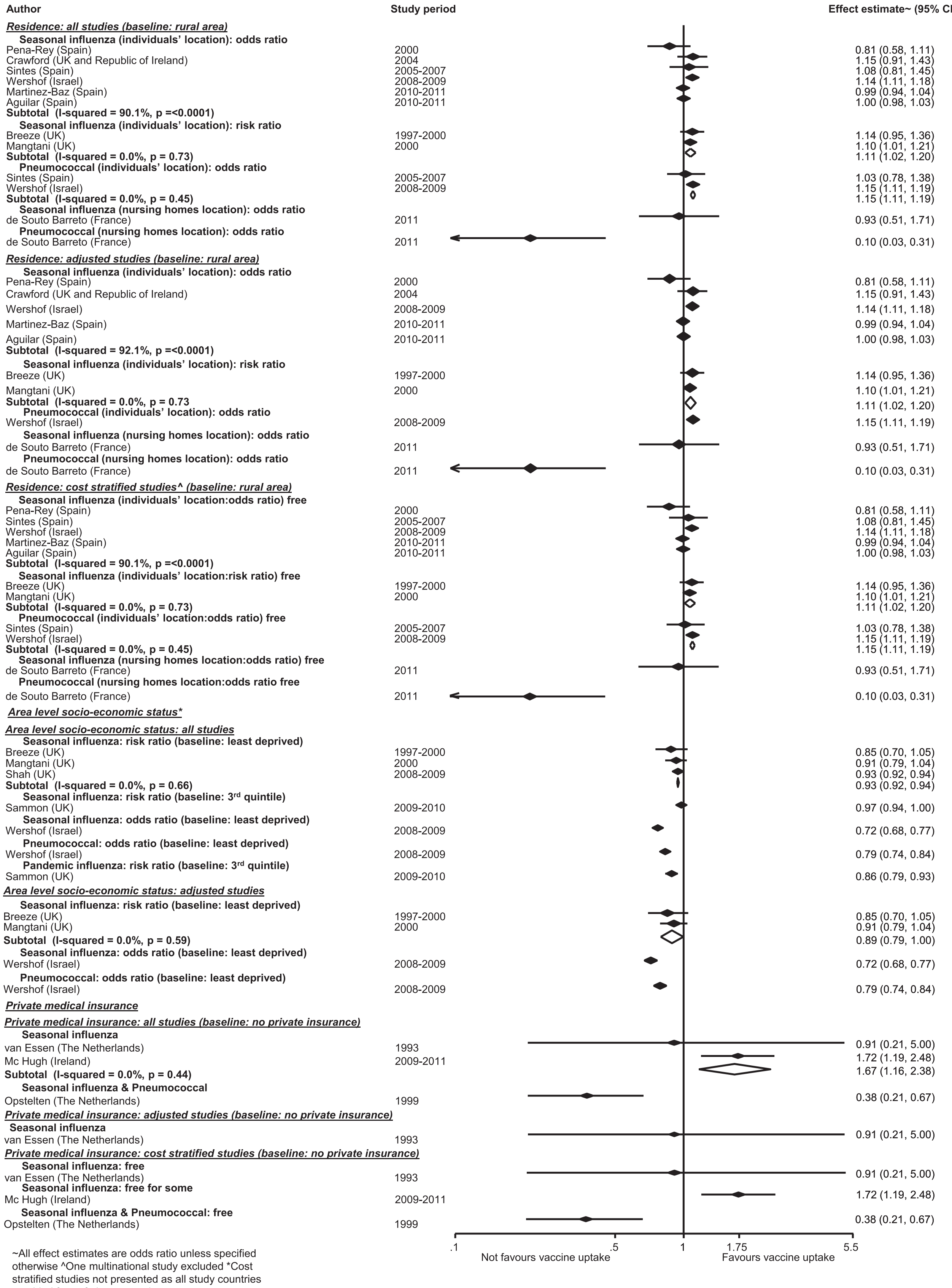
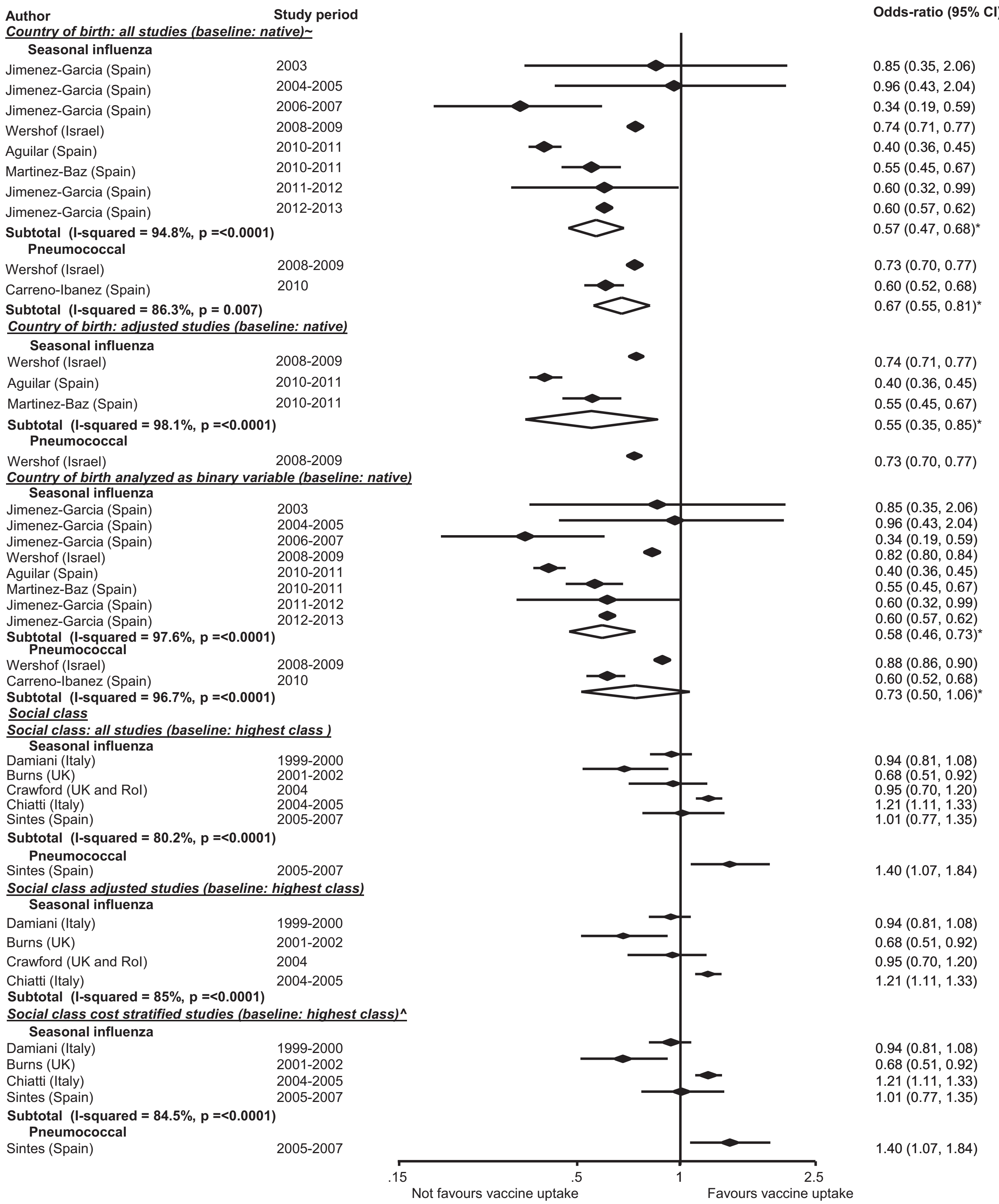


Fig. 3. Effect of residence, area level socio-economic status and medical insurance on vaccine uptake.



~Cost stratified studies not presented as all study countries offered free-of-charge vaccine
RoI Republic of Ireland *Weights are from random effects analysis
^ one multinational study excluded

Fig. 4. Effect of country of birth and social class on vaccine uptake.

those with private medical insurance was observed in the Irish study [47] where vaccination charges were means tested [40].

A Spanish study [16] that did not provide effect measures reported no evidence of association of private medical insurance with SIV uptake (Appendix-7).

3.2.8. Country of birth

Nine studies, all except one conducted in Spain, were considered for meta-analysis (Fig. 4). Overall, there was lower uptake of vaccination amongst immigrants irrespective of vaccine type, with uptake 43% and 33% lower for SIV and PV vaccines respectively (Fig. 4). The summary effect estimate was near-identical after restricting SIV studies to those with adequate adjustment of confounding, and after reclassifying country of birth in one study [43] as a binary variable (Fig. 4). Stratification based on vaccine costs was not required as all included countries offered free vaccinations.

Two studies from Israel with effect estimates were excluded from meta-analysis, one [32] used a different definition for country of birth (those born in Asia or Africa versus elsewhere) and the second used marginal probabilities to investigate immigration status; neither found an association with SIV uptake [31]. Two further studies did not provide effect estimates: an Israeli study [25] found statistical evidence for lower uptake of both SIV and PV amongst Russian speakers compared to Arabic speakers, whilst a German study found no evidence for lower SIV uptake amongst immigrants [15].

3.2.9. Social class/occupation

Five studies (SIV: n = 4, SIV and PV: n = 1) provided effect estimates for the association of social class with vaccine uptake (Fig. 4). There was no consistent effect seen for SIV uptake (I^2 = 80.2%), but the single study of PV uptake (from Spain) reported higher uptake amongst individuals from the lowest social class [28].

Between-study heterogeneity could not be explained after restricting to studies with adequate adjustment for confounding or stratifying by vaccine costs (Fig. 4), and this exposure could not be consistently re-categorised as a binary variable across studies to further explore between-study heterogeneity.

3.2.10. Religion

The one study that provided effect estimates [32], found no strong evidence for an association with SIV uptake (religious versus not religious: OR = 1.71 (95%CI:0.96–3.03)) Another study (no effect estimates provided) [25] reported an association of SIV uptake with place of residence that varied with individuals' religion: amongst Jewish individuals higher uptake was noted in rural areas compared to urban areas ($p < 0.04$) whilst the association was reversed amongst Muslim individuals(with higher uptake in urban (80%) compared to rural areas (76%) (Appendix-7).

3.3. Meta-regression

There were sufficient studies (n = 12) to further examine the reasons for heterogeneity for the association of education with SIV uptake [15,16,28,32–37,48–50].

Multivariable meta-regression analyses included vaccination cost (free versus paid), confounding bias (low or high risk of bias) and 'over-adjustment' (studies that included in multivariable analyses variables hypothesized to be on the causal pathway between education and vaccine uptake). There was strong evidence ($p < 0.0001$) that the association of education with vaccine uptake varied with vaccination costs: in studies from countries (Sweden and Norway) where the population had to pay for vaccination, the ORs were 1.93 times the ORs reported from countries where vaccines were available free-of-charge for some (e.g. Ireland) or all (e.g. Spain) of the population. There was some evidence ($p = 0.05$) that between-study heterogeneity could be explained by risk of confounding bias, but little evidence that it was explained by 'over-adjustment' ($p = 0.2$). All education studies reported ORs and investigated SIV vaccine uptake, and thus the type of effect estimate and vaccines were not examined. Each study categorised education differently making it infeasible to examine this the meta-regression model. Analyses were repeated after excluding the study reporting both SIV and zoster uptake (n = 11), revealing similar results, but the effect 'over-adjustment' could not be investigated in the reduced model due to collinearity.

4. Discussion

To our knowledge, this is first review to quantify systematically the effect of a wide range of social factors on vaccine uptake amongst older individuals in Europe. Not living alone, an important social factor for this population group, was associated with higher SIV (39%) and PV (71%) uptake. Marital status, which is likely to be highly correlated with living alone, also showed lower uptake of both SIV and PV amongst unmarried individuals in all except one study. Other characteristics associated with lower vaccine uptake included being an immigrant (43% and 33% lower uptake for SIV and PV respectively), and lower area-level deprivation (7% lower uptake for SIV), highlighting that vaccination inequalities continue to exist despite availability of free vaccines. The direction of effect for all these factors remained even after restricting the analyses to studies with low risk of confounding bias.

No consistent direction of effect was observed for education. However, restricting analyses to adequately adjusted studies showed a small (5%) overall increase of SIV uptake with higher education. The effect of income also initially appeared heterogeneous, but amongst adequately adjusted studies that measured ORs (and excluding the single study in which vaccines were not universally supplied free-of-charge), the effect of higher income was consistent with that of higher education. These findings concur with those from a study of individuals aged $\geq$50 years from 13 European countries, which reported lower utilisation of a range of preventative services, including SIV uptake, amongst those with lower income and education [51]. In contrast, there was no evidence of an effect of income for the two studies measuring RRs. This could in part be explained by ORs having more extreme values than RRs when the outcome is common [52]. Stratification by vaccine costs revealed contrasting results for education and income: unlike education, income-related inequalities persisted, with higher uptake amongst those with higher income in countries offering free-of-charge vaccination. Contrarily in Ireland (where vaccination payment are means-tested) [40], both lower income and lower education were associated with higher uptake.

Overall there was no consistent effect of social class on vaccine uptake; between-study heterogeneity could have resulted from differences in the definition used for this exposure, although data were not available to explore this further. The role of urban residence with vaccine uptake was also variable; although summary estimates for two SIV studies (measuring RRs) and for two PV studies (measuring ORs) indicated higher uptake in urban areas, most of the SIV studies showed inconsistent direction of effects for urban residence.

Some important determinants such as religion and access to private medical insurance were not consistently included across studies from different countries. Given increasingly diverse populations and differences in provision of healthcare across Europe, these determinants could be important end-points for future studies.

Living alone was identified as an important factor associated with lower vaccine uptake in this review and may be an indicator for social isolation [53]. Living alone has emerged as an important determinant of health in older populations. For example, in a 2010 systematic review, lack of social relationships was associated with a 50% increase in mortality, comparable to the increased risk resulting from smoking or obesity [54]. Similarly, a 2015 meta-analysis [53] found that living alone was associated with 32% higher mortality (OR 1.32, 95%CI 1.14–1.53). In 2013, approximately 13% of households in the European Union comprised individuals aged $\geq$65 years living alone [55]. With an increasingly ageing population, the numbers living alone are likely to rise, increasing the importance of preventative measures such as vaccinations. Interestingly in our review, living with children or increasing housing density in some studies was associated with lower SIV uptake, suggesting that not living alone also may have different effects on vaccine uptake depending upon household composition.

Our analysis is an important update (with nineteen additional studies) of the previous 2011 systematic review by Nagata et al., which assessed only SIV uptake amongst older individuals [6]. Our review extends the scope to all vaccines given routinely to older individuals, has provided the results of quantitative syntheses, and has carried out extensive investigation of between-study heterogeneity. Our review also included religion as a social factor, incorporates studies prior to 2011 that were not presented in this earlier review [6], and provides more detailed analyses of social factors such as country of birth, individual components of socio-economic position, marital status and living alone.

Our review has several strengths. A comprehensive search strategy was utilised to identify pertinent social determinants of SIV and other vaccine uptake amongst older populations. Stringent criteria for quality assessment were followed. Meta-analyses to obtain summary estimates, and detailed exploration of the causes of between-study heterogeneity using *a priori* stratification criteria and meta-regression, allowed insight into the complex relationships between various social determinants and vaccine uptake in different countries.

Our review also has some limitations. A number of the studies included in the review had high risk of confounding bias, and restricting analyses to studies presenting adequately adjusted effect estimates led to a reduced number of studies in these analyses. Our use of stratification revealed some causes of between-study heterogeneity. Meta-regression analysis, to further explore the causes for heterogeneity for factors other than education was not feasible due to insufficient numbers of studies. The multivariable meta-regression analyses for the effect of education indicated that both vaccine costs and confounding bias independently explained some of the heterogeneity in results. In this review the effect of social isolation or loneliness on vaccine uptake was not examined; individuals living alone may have strong social networks. The relationship between social isolation and vaccine uptake can perhaps be explored in future research. In addition, we hypothesized correlations between some social factors based on our conceptual framework, but it is possible that other complex inter-relationships between these factors may exist. Finally, we included only studies published in English language, which could have excluded some relevant data.

5. Conclusion

This is the first systematic review that quantifies the association of living alone, an important social factor for older individuals, with lower vaccine uptake. This, along with quantification of other factors such as immigration status, deprivation and education level, will help to target older individuals for interventions to mitigate vaccination inequalities. This review has also highlighted the limitations of existing studies in terms of study quality and between-study heterogeneity. As the role of social factors becomes increasingly recognised for equitable healthcare delivery, the findings of this review should provide guidance to healthcare providers for addressing vaccination inequality amongst older individuals. Our review should also help researchers to design future studies of higher quality with potentially more standardised definitions of social factors.

Conflict of interest statement

We have no conflict of interest to declare.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.03.013.

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