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SYSTEMATIC REVIEWS AND META-ANALYSES

Influenza: Diabetes as a risk factor for severe related-outcomes and the effectiveness of vaccination in diabetic population. A meta-analysis of observational studies☆

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Abstract *Aims:* In order to better define the need for influenza vaccination in people with diabetes (DM), we collected all available evidence on the effect of DM as a risk factor for complications of both seasonal and pandemic influenza, and on the specific effectiveness of vaccines in patients with DM.
Data synthesis: Two distinct systematic searches on MEDLINE, Cochrane, ClinicalTrials.gov and Embase databases were performed, one for each metanalysis, collecting all observational studies and randomized clinical trials performed on humans up to May 31st, 2022. We retrieved 34 observational studies comparing risk for influenza complications in people with or without diabetes, and 13 observational studies assessing vaccine effectiveness on preventing such complications. Mortality for influenza and hospitalization for influenza and pneumonia resulted significantly higher in individuals with versus without DM, both when unadjusted and adjusted data are analyzed. In diabetic individuals vaccinated for influenza overall hospitalization, hospitalization for influenza or pneumonia and overall mortality are significantly lower in comparison with not vaccinated DM subjects, both when unadjusted and adjusted data were analyzed.
Conclusion: This systematic review and meta-analysis shows that: 1) influenza is associated with more severe complications in diabetic versus not diabetic individuals and 2) influenza vaccination is effective in preventing clinically relevant outcomes in adults with DM with a NNT (number needed to treat) of 60, 319, and 250 for all-cause hospitalization, specific hospitalization, and

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all-cause mortality, respectively. The identification of diabetic patients as the target of vaccination campaigns for influenza appears to be justified by available clinical evidence.

1. Introduction

Seasonal influenza is usually associated to mild and self-limiting symptoms in the general population, whereas the clinical course can be aggravated by complications in frail patients, such as the elderly and patients with chronic comorbidities [1]. Diabetes mellitus (DM) is a risk factor for more serious outcomes attributable to influenza [1]. Annual seasonal influenza vaccination has been found to be effective for preventing influenza virus infection and its severe complications (all-cause mortality and hospitalization for pneumonia), also in people with DM [2].

Several national [3] and international [4,5] guidelines recommend influenza vaccination in individuals with DM. A retrospective cohort study suggested a protective effect of influenza vaccination also against COVID-19- associated severe outcomes [6]. During the 2020−2021 season, influenza vaccination coverage rate significantly increased in many countries [7] as a public health strategy to prevent the occurrence of respiratory syndromes that could be confounded with COVID-19. Nevertheless, data from many observational studies reported coverage rates for influenza vaccination lower [8], or much lower [9] than recommended among adults with DM.

Clinical decisions should be based on the systematic collection and assessment of available evidence from properly designed clinical studies. In order to better define the need for influenza vaccination in people with diabetes, we collected all available evidence on the effect of DM as a risk factor for complications of both seasonal and pandemic influenza, and on the specific effectiveness of vaccines in patients with DM.

2. Methods

The meta-analyses followed the criteria of Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines. Review Protocols were submitted for registration to the PROSPERO website (CRD42022335506 and CRD42022335313, respectively).

2.1. Search strategy

Two distinct systematic searches on MEDLINE, Cochrane, ClinicalTrials.gov and Embase databases were performed, one for each metanalysis, collecting all observational (cohort and case-control) studies and randomized clinical trials performed on humans up to May 31st, 2022. Search terms were reviewed by all collaborators; the full search strings are reported in Table 1S of supplementary materials. Further studies were manually searched in references from retrieved papers.

2.2. Selection criteria

To be eligible, an item had to be an original report in English of a study enrolling adults with type 1 and/or type 2 DM, assessing selected outcomes.

2.2.1. Metanalysis on diabetes as a risk factor for complications of influenza

Observational studies of any duration or size were included, provided that they reported data about specific main and additional outcomes, comparing diabetic versus not-diabetic individuals with laboratory confirmed both seasonal and pandemic influenza infection during a period of known diffusion.

2.2.2. Metanalysis on influenza vaccine effectiveness in diabetes

Studies (either observational studies or randomized trials) were included if data about specific main and additional outcomes were available, comparing influenza-vaccinated and non-vaccinated diabetic individuals with laboratory-confirmed both seasonal and pandemic influenza infection during a period of known circulation.

2.3. Endpoints

2.3.1. Metanalysis on diabetes as a risk factor for complications of influenza

Differences between diabetic and not diabetic adults in all-cause mortality, all-cause hospitalization, and ICU-admission were the main endpoints, whereas secondary outcomes included differences in hospitalization for influenza or pneumonia, influenza mortality, effects on glycaemic control and cardiovascular mortality.

2.3.2. Metanalysis on influenza vaccine effectiveness in diabetes

Differences between vaccinated and not vaccinated diabetic adults in hospitalization for any causes, hospitalization for pneumonia, all-cause mortality, ICU-admission were chosen as primary endpoints; effects on glycaemic control and cardiovascular mortality were enlisted as secondary endpoints.

2.4. Data collection

Titles and abstracts were screened independently by the authors, and potentially relevant articles retrieved in full text. For all published trials, results reported in published papers and supplements were used as the primary source of information. When the required information on protocol or outcomes was not available in the main or secondary

publications, an attempt at retrieval was performed consulting the clinicaltrials.gov website. The identification of relevant abstracts and the selection of studies were performed independently by all the authors. Data extraction and conflicts resolution were performed by two investigators (I.D. and G.A.S.). The Cochrane Risk of Bias tool was used to assess risk of bias in Randomized Controlled Trials (RCTs) and the Newcastle-Ottawa Scale was used to assess the risk of bias in observational studies. PRISMA flow diagram for search and selection processes of the meta-analysis has been applied (see Supplementary materials).

2.5. Statistical analyses

Odds ratios and 95% confidence intervals (95% CIs) were either calculated or extracted directly from the publications. Unadjusted or adjusted odds ratio are meta-analyzed separately. Pre-planned separate analyses were performed for randomized trials, whenever possible.

If data from more than one study on a given outcome were available, a meta-analysis using a random-effects model as the primary analysis was performed. Heterogeneity was assessed by using I^2 statistics. Funnel plots were examined in order to estimate possible publication/disclosure bias, and Egger test was performed to exclude significant publication bias. All analyses were performed using Review Manager 5.3.5.

Sensitivity analyses were performed, whenever possible, if significant heterogeneity was detected, including leave-one out analysis, or subgroup analysis for different time or country of observation.

3. Results

3.1. Metanalysis on diabetes as a risk factor for complications of influenza

3.1.1. Study characteristics

Fig. 1S of Supplementary materials reports the trial flow summary. Of the 1336 items, after removing duplicates, 1216 were selected for retrieval of full text. Of those, 987 records were excluded because inclusion criteria were not satisfied. Only 34 studies fulfilled the inclusion criteria overall enrolling 5,595,749 patients with DM, and 132,551,745 without. All the retrieved studies were observational studies, with no randomized trial. Confounding factors used for statistical adjustment in each of included studies are reported in Table 1. Risk of bias table is reported in Table 5S.

3.1.2. All-cause mortality, all-cause hospitalization

None of the included studies reported data on these outcomes.

3.1.3. Hospitalization for influenza or pneumonia

Six studies [10–15] reported unadjusted odds ratio for this endpoint whereas only in five manuscripts [10–14] adjusted odds ratio was available. DM diagnosis was associated with a significant higher hospitalization for influenza or pneumonia in respect to individuals without DM (unadjusted Odds Ratio; OR 5.08 [3.45; 7.50]; $p < 0.00001$) and the association was confirmed when available adjusted odds ratios were analyzed (Fig. 1) A leave-one out analysis was made, ruling out significant influence of single studies (Table 6s).

3.1.4. ICU-admission

Ten of the included studies reported unadjusted odds ratio [10,11,16–23] and only six [10,16,18,20,22,23] adjusted odds ratio for ICU admission. DM diagnosis was associated with a significant higher admission to ICU in respect to individuals without DM (unadjusted Odds Ratio; OR 1.71 [1.15; 2.53]; p 0.008). A leave-one out analysis was made, ruling out significant influence of single studies (Table 6s). The association was no longer significant when available adjusted odds ratios were analyzed (adjusted Odds Ratio; AdjOR 1.69 [0.87; 3.29]; $p = 0.12$) (Fig. 2).

3.1.5. Case fatality rate (CFR)

Unadjusted odd ratios were retrieved in 17 studies for this outcome [11,16,18,19,22,29–40]. Funnel plot and Egger's test ruled out publication bias (Fig. 3S, $p = 0.25$). DM was associated with significant increase of CFR, and subjects living with diabetes with diagnosis of influenza resulted still at high lethality risk also following analysis of adjusted odd ratios available in 7 studies [16,32,35,37–39,41] (Fig. 3). Leave-one out analysis was performed, excluding significant influence of single studies (Table 6s). Subgroup analysis showed that studies performed after 2013 show a reduced increase in risk attributable to DM in comparison with studies performed before 2013 (Fig. 6S), whereas no difference in risk between studies performed in different countries was found (Fig. 7S).

3.1.6. Mortality for influenza

Five studies [24–28] reported adjusted odds ratio for this endpoint. DM was associated with a significant higher mortality for influenza in comparison to not diabetic individuals (Fig. 3). A leave-one out analysis excluded significant influence of single studies (Table 6s) Subgroup analysis showed that studies performed after 2013 show a significant reduction in risk in people with DM, unlike studies performed before 2013 (Fig. 8S).

3.1.7. Glycemic control and cardiovascular mortality

None of the included studies reported data on these outcomes.

3.2. Metanalysis on influenza vaccine effectiveness in diabetes

3.2.1. Study characteristics

Fig. 2S of Supplementary materials reports the trial flow summary. Of the 1107 items, after removing duplicates, 1024 were selected for retrieval of full text. Of those, 195 records were excluded because inclusion criteria were not satisfied. Only 13 studies fulfilled the inclusion criteria overall enrolling 1,080,619 individuals. The list of excluded studies is reported in Table 4S, risk of bias table is reported in Table 5S.

Table 1 Characteristics of the included studies comparing influenza prognosis in people with and without diabetes mellitus. Hosp = hospital based; Pop = population based; Retro = retrospective; CC=Case-Control; Prosp = Prospective, CVD = cardiovascular disease, BMI=Body mass index, LDH = Lactate dehydrogenasis, DM = Diabetes Mellitus, M = Proportion of Men, >65 = proportion of those older than 65 years, NR = Not reported N=Number.

Study	Duration (weeks), Years of observation		Country	Setting	Type	Adjustments	Age	M	>65	Influenza Strain	Number	
											DM	not DM
Weng, 2019	260	2005–2010	TWN	Hosp	Retro	Age, sex, hospital level, comorbidities	*NR*	59.8	45	*NR*	16,416	66,811
Allard, 2010	5	2009	CAN	Hosp	Retro	Age, sex, cvd	*NR*	*NR*	*NR*	H1N1	22	140
Cortes Garcia, 2011	26	2009	SPA	Hosp	CC	–	58	51.6	34.5	H1N1	252	252
Yokota, 2011	26	2009–2010	BRA	Hosp	Retro	Age, sex	33	50	*NR*	H1N1	23	102
Ward, 2011	52	2009	AUS	Pop	CC	Age, sex	45	36.7	17.3	H1N1	96	809
Gilca, 2011	16	2009	CAN	Pop	CC	Age, sex, smoking, education, job, comorbidities, vaccination, pregnancy, admission delay	28	46	8	H1N1	50	656
Chudasama, 2010	26	2009–2010	IND	Hosp	Retro	–	27	51.5	*NR*	H1N1	27	247
Wilking, 2010	52	2009–2010	GER	Pop	Retro	–	*NR*	*NR*	*NR*	H1N1		
Tutuncu, 2010	12	2009	TUR	Hosp	Retro	–	47.9	45.9	23	H1N1	19	55
Xi, 2010	12	2009	CHI	Hosp	Retro	LDH levels	43	58	*NR*	H1N1	20	135
Harris, 2010	21	2009	AUS	Pop	Retro	Age sex, race	21	47.5	*NR*	H1N1	20	157
Venkata, 2010	26	2009	USA	Hosp	Retro	–	47	50	*NR*	H1N1	21	45
Cutter, 2010	6	2009	SGP	Pop	Retro	–	*NR*	*NR*	7	H1N1	169	1179
Koegelenberg, 2010	5	2009	ZAF	Hosp	Retro	–	39.5	11.1	*NR*	H1N1	6	13
Sheng Kwang Gett, 2010	33	2009	USA	Pop	Retro	Age, sex comorbidities, ethnicity, admission delay	*NR*	53	1	H1N1	21	514
Breitling, 2016	936	1988–2006	USA	Pop	Prosp	Age, sex, BMI, smoke, education	*NR*	*NR*	*NR*	*NR*	1452	18,331
Li, 2018	572	1999–2010	USA	Pop	Retro	Age, sex, race, income, education	*NR*	47.6	*NR*	*NR*	2936	13,117
Chien-Ming, 2017	78	2015–2016	TWN	Hosp	Retro	–	65.5	61.6	50.4	All	51	74
Ishiguro, 2017	884	1999–2016	JPN	Hosp	Retro	Age, sex, BMI, comorbidities	69	72	*NR*	*NR*	27	183
Bouneb, 2018	312	2010–2016	TUN	Hosp	Retro	–	53	60	*NR*	*NR*	13	27
Pujol, 2016	87	2009–2011	SPA	Pop	CC	–	*NR*	*NR*	*NR*	*NR*	175	2070
Van Kerkhove, 2015	676	2000–2012	USA	Hosp	Retro	Age, sex, race, comorbidities, obesity vaccination	32	89.5	*NR*	*NR*	243	10,810
Valdez, 1999	156	1987–1989	USA	Pop	Retro	Age, sex, race	*NR*	*NR*	12.4	*NR*	5,571,962	132,417,685
Nateghian, 2020	26	2015–2018	IRN	Pop	Retro	Age, sex, comorbidities, strain, pregnancy, symptoms, season, diabetes duration.	41	45	*NR*	H1N1,H3N2,B	927	10,153
Zou, 2020	44	2017–2018	CHI	Hosp	Retro	Age, sex, smoke, comorbidities	63.5	64.1	47.3	H1N1,H3N2,B	44	360
Zhang, 2013	14	2009	CHI	Hosp	Retro	–	34	49.7	*NR*	H1N1	164	1977
Suryaprasad, 2013	11	2009	USA	Hosp	Retro	–	*NR*	35	8	H1N1	23	145
Ganatra, 2013	26	2009	USA	Hosp	Retro	Obesity	*NR*	*NR*	*NR*	H1N1	72	247
WIE, 2013	34	2011–2012	KOR	Pop	Retro	–	53	39.9	49.4	H3N2	70	780
Balaganesakumar, 2013	26	2010	IND	Pop	CC	Age, sex, comorbidities	26	49	*NR*	H1N1	43	237
Baumgartner, 2012	40	2009	ARG	Pop	Retro	Age, sex	30	48	17.2	H1N1	22	728
Chowell, 2012	21	2009	MEX	Hosp	Retro	Age, sex, treatment, comorbidities, admission delay	*NR*	42.9		H1N1	313	3313
Fuhrman, 2010	20	2009	FRA	Hosp	Retro	–	*NR*	52	7	H1N1	27	217
Beumer, 2019	26	2015–2016	NET	Hosp	Retro	–	*NR*	55	26	H1N1, B	23	176

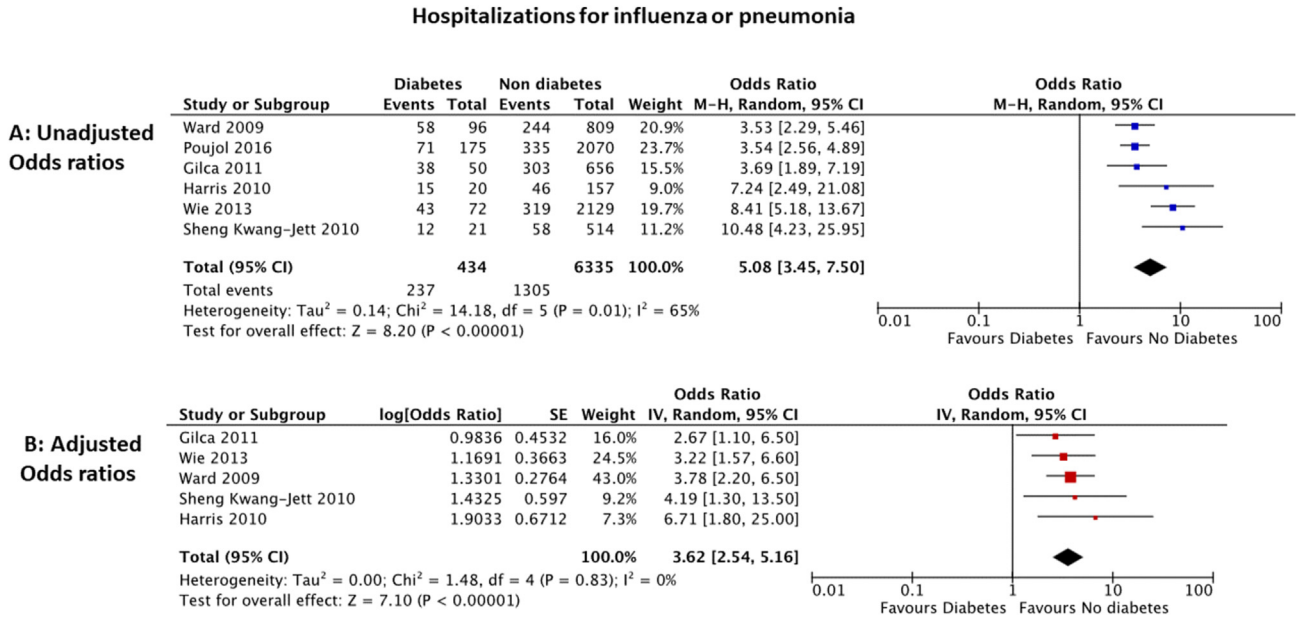

Figure 1 Differences in Hospitalizations for influenza or pneumonia between patients with or without diabetes (forest plot; IV = Inverse Variance Random = random effects CI = Confidence interval).

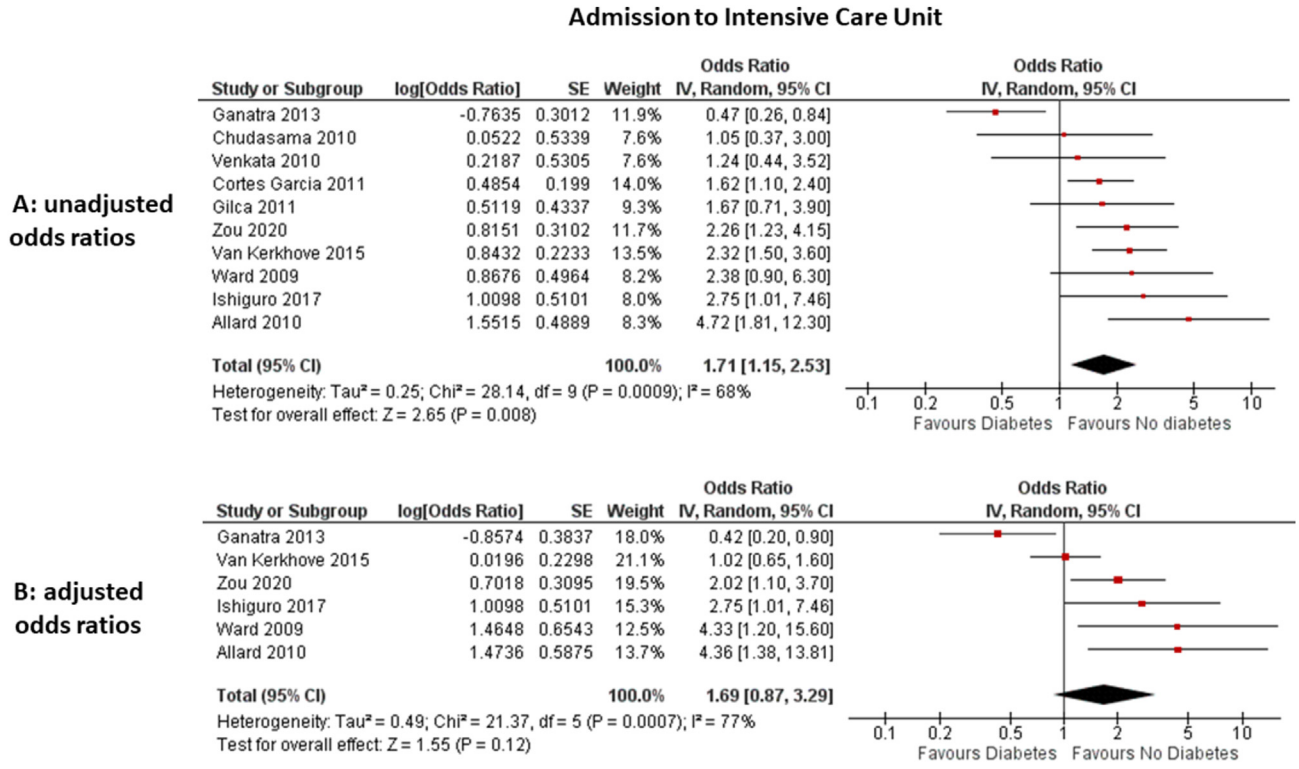

Figure 2 Differences in Admission to Intensive Care Unit between patients hospitalized for influenza between patients with or without diabetes (forest plot; IV = Inverse Variance Random = random effects CI = Confidence interval).

All the retrieved studies were observational studies, with no randomized trial. The main characteristics of included studies are reported in Table 2. Confounding factors used for statistical adjustment in each of included studies are reported in Table 2.

3.2.2. Overall hospitalization

Six of the included studies [42–46] reported unadjusted odds ratio and four [43,45–47] adjusted odds ratio for all-cause hospitalization. Influenza vaccination was associated with a significantly lower hospital admission in diabetic

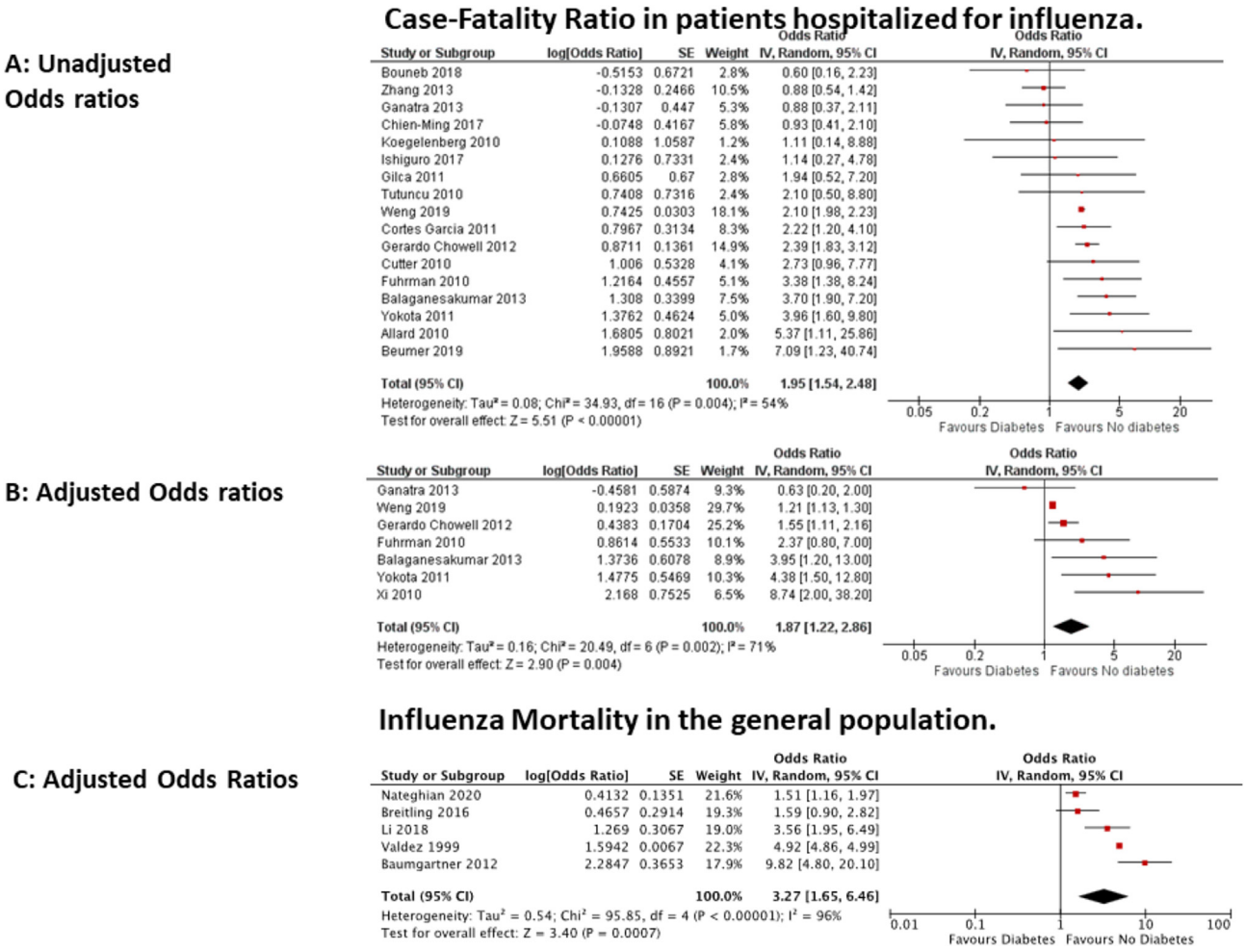

Figure 3 Differences in Case-Fatality Ratio between patients hospitalized for influenza with or without diabetes (forest plot; IV = Inverse Variance Random = random effects CI = Confidence interval).

individuals (OR 0.87 [0.80; 0.94]; p = 0.0006). A leave-one out analysis excluded significant influence of any single survey (Table 7s). From studies with available data [42,46] since the incidence in unvaccinated individuals was 0.17 and 0.15, the absolute risk reduction was 0.02 with a number needed to treat (NNT) of 60. When retrieved adjusted odds ratios were analyzed, vaccinated diabetic subjects resulted still protected against admission to hospital in comparison to diabetics not vaccinated against influenza (AdjOR 0.77 [0.69; 0.85]; p < 0.00001, Fig. 4).

3.2.3. Hospitalization for influenza or pneumonia

Four studies [43,45–47] reported unadjusted odds ratio for this endpoint whereas in six studies [43,45,47–50] adjusted odds ratios were available. Influenza vaccination was associated with a significant lower risk of hospitalization for influenza or pneumonia in respect to diabetic individuals not vaccinated (OR 0.77 [0.69; 0.85]; p < 0.00001, Fig. 5) and the association was confirmed following analysis of available adjusted odds ratios (AdjOR 0.63 [0.56; 0.72]; p < 0.00001, Fig. 5). A leave-one out analysis excluded excessive influence of single studies (Table 7s). From studies with available data [45,46,49] the incidence in unvaccinated individuals and vaccinated was 0.016 and 0.013, respectively, and the absolute risk reduction was 0.003, with a NNT of 319.

3.2.4. Overall mortality

Nine studies [42,43,45,46,49,51–54] reported unadjusted odds ratio for this endpoint; of those, seven studies [43,45,46,49,52–54] also reported adjusted odds ratio. Influenza vaccination was associated with a significant lower mortality for any cause in comparison to diabetic individuals not vaccinated against influenza both in unadjusted (OR 0.64 [0.44; 0.94]; p = 0.02 Fig. 6), and adjusted analysis (AdjOR 0.63 [0.55; 0.73]; p < 0.00001, Fig. 7). No difference was found between studies performed before or after 2010 (Fig. 9S), or from trials performed in different countries (Fig. 10). A funnel plot excluded publication bias (p = 0.15 at Egger's regression, for unadjusted analysis; p = 0.27 at adjusted analysis). A leave-one out analysis excluded significant influence of single studies (Table 7s) From studies with available data [42,45,46,49,52–54], estimated all-cause mortality was 0.056 and 0.060 in vaccinated and unvaccinated patients, respectively, with an absolute risk reduction of 0.004 and a NNT of 250.

Table 2 Characteristics of the included studies comparing influenza prognosis in people with diabetes mellitus with or without prior influenza vaccine. Hosp = hospital based; Pop = population based; Retro = retrospective; CC=Case-Control**;** Prosp = Prospective, CVD = cardiovascular disease, BMI=Body mass index, LDH = Lactate dehydrogenasis, DM = Diabetes Mellitus, M = Proportion of Men, >65 = proportion of those older than 65 years, NR = Not reported N=Number Vacc. = vaccinated Unvacc. = unvaccinated.

Study	Duration (weeks), Years of observation		Country	Type	Age	Season	M	>65	Adjustments	N	
										Vacc.	Unvacc.
Heymann, 2004	52	2000–2001	ISR	Retro	73	Oct–Feb	46.7	100	None	7591	7949
Lau 2013 (18–65 and over 65 cohorts are reported separately)	416	2000–2008	CAN	Retro	53	Flu season	52	0	Age, sex, socioeconomic data,	86,222	162,889
					74			100	comorbidities, n physician visits, pneumococcal vaccination	96,463	83,452
Looijmans, 2006	52	1999–2000	NET	CC	69.6	Dec–Mar	39.7	74.9	Age, sex, comorbidities	1480	273
Martinez-Bas, 2020	312	2013–2019	SPA	CC	nr	Flu season	59	84	Age, season, comorbidities, pneumococcal vaccination	982	588
Modin, 2020	468	2007–2016	DEN	Retro	58.7	Dec–Mar	52.9		Comorbidities, age, sex, medications, socioeconomic	113,397	122,154
Rodriguez Blanco, 2012	208	2002–2005	SPA	Retro	74.4	Jan–Apr	41.2	100	Age, sex, comorbidities	1064	1586
Rondy, 2017	26	2015–2016	EUR	CC	77	Flu season	53	100	Age, sex, comorbidities, country, smoke	183	362
Ruiz, 2019	208	2009–2013	NOR	Retro	65	Flu season	55	nr	Sex, age, education, country	88,862	60,570
Sanchez Munoz-Torrero, 2002	52	2000–2001	SPA	CC	71.5	Jan–Apr	53.5	100	Age, sex, comorbidities	136	91
Schade, 2000		1997	USA	Retro	nr	nr	nr	90.3	Age, sex, comorbidities	15,471	9533
Vamos, 2016	364	2003–2010	UK	Retro	nr	Flu season	53.9	nr	Age, sex, comorbidities, BMI, blood pressure, year, socioeconomic, smoke, duration of diabetes, HbA1c, medications, pneumococcal vaccination	64,569	43,029
Wang, 2007	46,8	2001	TWN	Retro	nr	Jan–Oct	54.6	100	None	35,637	67,061
Wang, 2013	416	2002–2009	TWN	CC	73.1	nr	50.3	100	Age, sex, comorbidities	4571	4454

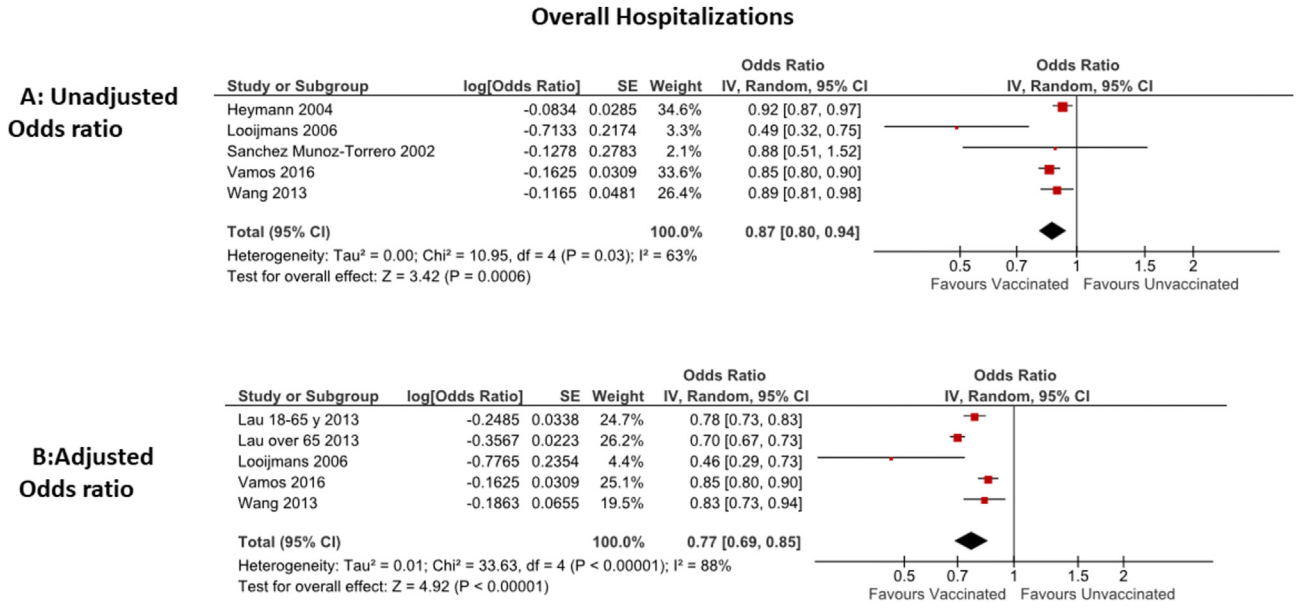

Figure 4 Differences in overall hospitalizations between vaccinated or unvaccinated patients with diabetes (forest plot; IV = Inverse Variance Random = random effects CI = Confidence interval).

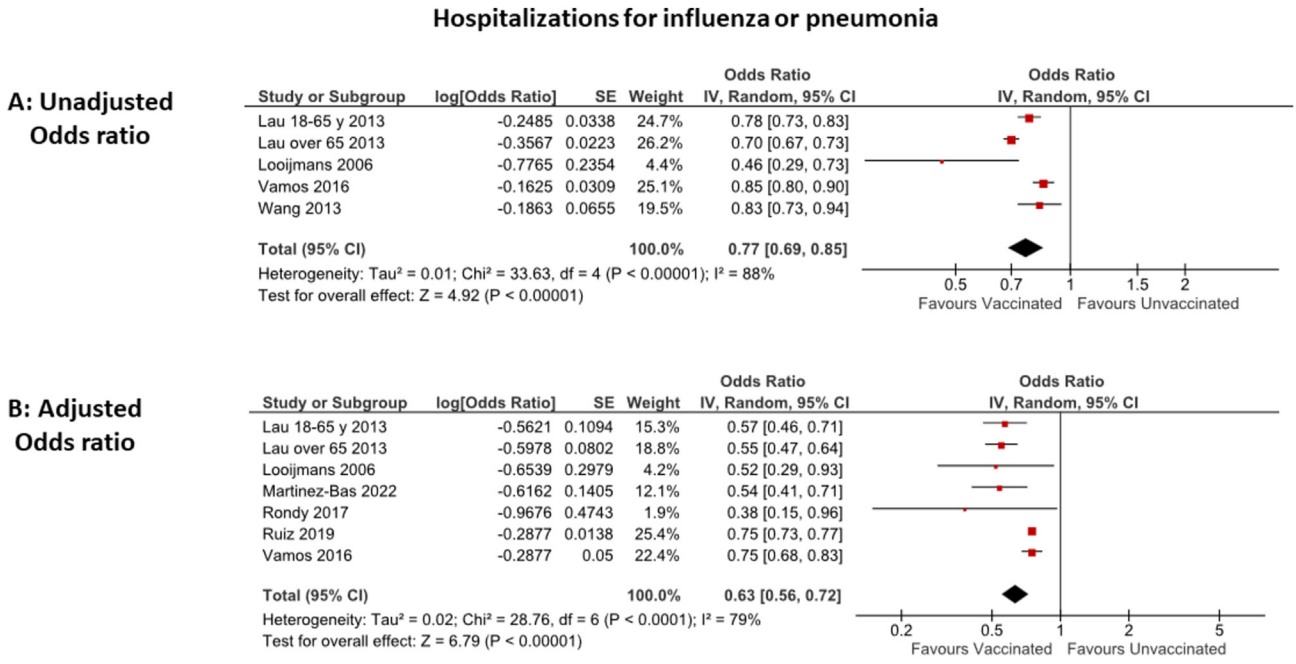

Figure 5 Differences in hospitalizations for influenza or pneumonia between vaccinated or unvaccinated patients with diabetes (forest plot; IV = Inverse Variance Random = random effects CI = Confidence interval).

3.2.5. ICU-admission, glycemic control and cardiovascular mortality

None of the included studies reported data on these specific outcomes.

4. Discussion

The present meta-analysis confirms that DM is associated with an increased risk of complications of influenza, and that vaccination is effective for preventing such complications in people with diabetes, with a NNT of 60, 319, and 250 for all-cause hospitalization, specific hospitalization, and all-cause mortality, respectively.

Available observational studies show that DM is associated with a relevant increase in risk for complicated both seasonal and pandemic influenza. In particular mortality and hospitalization rates for influenza are more than three-fold higher than in the general population, even after adjusting for the most relevant confounders, including age. In addition, DM is associated with a smaller,

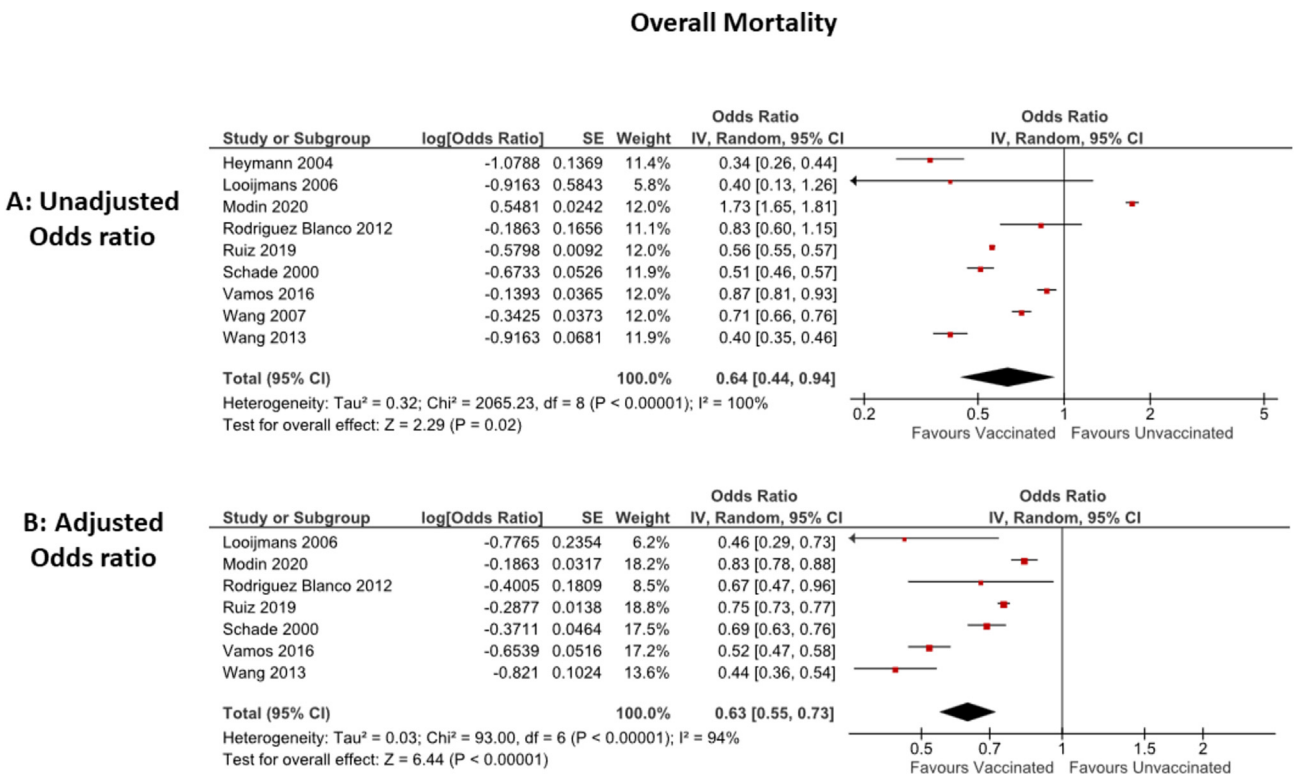

Figure 6 Differences in overall mortality between vaccinated or unvaccinated patients with diabetes (forest plot; IV = Inverse Variance Random = random effects CI = Confidence interval).

but significant, increase in case fatality among patients hospitalized for influenza. Admission to ICU for influenza is higher in patients with DM in unadjusted analyses; the difference between patients with DM and non-diabetic subjects is no longer significant after adjusting for confounders, but this result could depend on the relative paucity of available studies, as well as on the heterogeneity of variables included in multivariate models. A previous meta-analysis exploring differences in influenza-related outcomes between people with and without diabetes reported an increased risk of overall hospitalizations, with no significant difference in incidence of pneumonia and all-cause mortality; however, the smaller number of available studies at the time of that meta-analysis did not allow a reliable assessment of the effects of diabetes on influenza-related outcomes [1].

The determination of actual infection rates, in people with DM and in the general population, is problematic; however, it appears plausible that DM interferes with prognosis, rather than with risk for infection [55]. The mechanisms underlying this associations, which are beyond the aim of this paper, could include co-infections with other agents, impairment of immune responses, chronic inflammation associated with hyperglycemia and/or insulin resistance. To date, there is no evidence that a more accurate treatment of diabetes is an effective means of preventing the complications of influenza.

Vaccines for influenza appear to determine a significant improvement of related outcomes in patients with DM. Hospitalization rates are reduced by approximately 25% in adjusted analyses; the effect on the risk for specific mortality appears to be even wider, with little difference between adjusted and unadjusted analyses. A previous meta-analysis of observational studies, restricted to seasonal influenza, reported similar improvement in outcomes, including a much smaller number of studies [56]. The same meta-analysis suggested that some outcomes could have been improved only in elderly (>65 years) patients, but the amount of available data in subjects aged less than 65 years was too small to draw any reliable conclusion [56]. Only two studies [42,47] provided comparative data on the efficacy of influenza vaccine in people with or without DM, both finding no significant difference as regards to prevent all-cause hospitalization; no data were available for the other outcomes. A further meta-analysis [57], with a design more similar to that of the present paper, but limited to all-cause mortality and hospitalization for pneumonia, provided similar estimates, but on a smaller number of studies, since some more recent investigations [49,50,52] were not yet available at the time of the literature search. The estimation of absolute risk reduction allowed the calculation of numbers needed to treat to avoid one hospitalization or one influenza-related death, thus providing a base for the assessment of cost-benefit ratio.

These data are derived from observational studies, with the possible effect of residual confounding bias: in fact, the characteristics of individuals who underwent vaccination could be different from those of unvaccinated patients with DM, possibly interfering with the estimates of effectiveness. It is possible that patients with greater adherence

to recommendations, who are more health-conscious, or who are referring to more accurate physicians, have a greater chance of being vaccinated; those characteristics could all be associated with improved outcomes, producing an overestimation of the effectiveness of vaccines. On the other hand, it is plausible that physicians are more prone to recommending vaccination in patients with more severe comorbidities or other conditions interfering with the prognosis of influenza, for which adjustments were not possible; therefore, the effectiveness of vaccines could have been underestimated.

The relevant reduction of all-cause mortality, all-cause and cause-specific hospitalization associated with influenza vaccination in adults with diabetes, shown by this meta-analysis, is consistent with the benefits reported by a metanalysis of observational studies in the elderly population, irrespective of diabetes [58]. Few placebo-controlled RCTs with influenza vaccine in elderly (none of which was specifically performed in diabetic individuals, or provided subgroup analyses for patients with diabetes) have been performed; none of the available trials was sufficiently powered to investigate hard outcomes, such as mortality and hospitalization [59–61]. To our knowledge, only one metanalysis of randomized clinical trials was performed in individuals with cardiovascular disease, showing a significant reduction of cardiovascular events and cardiovascular mortality [62].

Several limitations should be considered in the interpretation of these results. The first important limitation concerns the unavailability of data for specific subgroups (age, sex, type of diabetes) or pre-specified outcomes (data on glycemic control and cardiovascular mortality). Therefore, it is not possible to identify higher-risk individuals among people with diabetes. A further limitation is represented by the heterogeneity in the definition of events (e.g., cause-specific hospitalization or cause-specific mortality); however, this limitation does not apply to all-cause hospitalization or all-cause mortality. In addition, although most countries have influenza vaccination policies for high-risk adults, including those with DM, the countries where these included studies enrolled their participants showed relevant differences about influenza vaccination coverage in patients with diabetes, ranging from about one half in Italy [9] to about two thirds in United States [8]. A confounding bias related to previous pneumococcal vaccination is also possible, since one of the most frequent complications of influenza is a pulmonary pneumococcal infection; in fact, only three of the included studies [45,47,50] made adjustment on the pneumococcal vaccine in order to evaluate influenza vaccine effectiveness. A further limitation should be considered: in order to investigate diabetes as a risk factor and influenza vaccine effectiveness, we analyzed data both from pandemic and different seasonal influenza strains. Notably, only 6 of the included studies [45,47,50–53] assessed the effectiveness of influenza vaccination in more than one season.

In conclusion, the present systematic review and meta-analysis shows that: 1) influenza is associated with more severe complications in diabetic versus not diabetic individuals and 2) influenza vaccination is effective in preventing clinically relevant outcomes in adults with DM. The identification of patients with diabetes as the target of vaccination campaigns for influenza appears to be justified by available clinical evidence.

Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Authors' contributions

ID and GAS were involved in design, data collection, analysis and writing manuscript.

AC, RF, GG, VS, ST, OP were involved in data collection and manuscript revision.

EM was involved as the external reviewer of the working Group in design, analysis, manuscript revision.

The manuscript was drafted, revised and approved by all the authors in accordance with ICJME standards for authorship. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Funding and data transparency

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.03.016.

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