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REVIEW

Systematic review of peptic ulcer disease incidence rates: do studies without validation provide reliable estimates?†

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ABSTRACT

Purpose Incidence rate (IR) estimates for peptic ulcer disease (PUD) vary widely among studies. We conducted a systematic review to quantify and examine the discrepancies.

Methods Of 4780 articles identified from PubMed and EMBASE databases, 31 published in the last three decades that had reported IRs of PUD in the general population were included. Random effects meta-analysis and meta-regression were performed to calculate pooled estimates and to identify sources of heterogeneity.

Results The pooled IR estimate per 1000 person-years was 0.90 (95% confidence interval: 0.78–1.04) for uncomplicated PUD, 0.57 (0.49–0.65) for peptic ulcer bleeding, 0.10 (0.08–0.13) for gastrointestinal perforations, and 3.18 (2.05–4.92) for nonspecific PUD. Within specific outcomes definitions, IR estimates were significantly lower in studies with restriction to hospitalized cases, case validation, and case ascertainment directly from hospital or clinical sources versus computerized health care databases. Younger age, female sex, and later calendar time were also associated with lower PUD incidence.

Conclusions We found that the IR of uncomplicated PUD was in the order of one case per 1000 person-years in the general population, and that the IR of peptic ulcer complications was around 0.7 cases per 1000 person-years. Comparisons of IR estimates among studies need to take into account disease definition and other study characteristics, particularly whether outcome validation was performed in computerized claims. The use of claims to identify PUD cases might overestimate the IR by around 45%. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—peptic ulcer disease; incidence; uncomplicated ulcer; upper gastrointestinal complications; bleeding; perforation

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INTRODUCTION

An accurate estimate of the incidence rate (IR) of peptic ulcer disease (PUD) in the general population is necessary to quantify the public health impact of any risk factor or preventive intervention. Knowing the IR is also useful to plan both research studies and health care resources. Most PUD studies provide only relative risks and require external baseline IR estimates to further determine the absolute burden of a given risk factor.[1] Moreover, published IRs may seem incongruent at first sight because they range from 0.03[2] to 11.29[3] cases per 1000 person-years for gastrointestinal perforations and PUD overall, respectively. Thus, to discuss the incidence of PUD, we first need to specify the definition of the outcome of interest.

However, even within PUD overall, up to a 13-fold difference in IR estimates has been reported.[3,4] Little is known about the factors responsible for such heterogeneity between studies, except for a decreasing trend over time[5–7] and a greater IR in North America than in Europe.[1] Unless we understand what is causing this discrepancy, IRs of PUD from different studies will remain incomparable and the generalizability of any individual finding questionable. Thus, it

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is crucial to disentangle the factors that affect the variability of PUD IR estimates.

Herein, we conduct a systematic review of studies published in the last three decades that provided IR estimates for PUD in the general population. The objective is to summarize the IR estimates reported for different PUD definitions and to explore sources of heterogeneity among studies.

METHODS

Search strategy and selection criteria

We searched PubMed and EMBASE for studies published from January 1980 to February 2009 that investigated the incidence of PUD with or without complications. PUD is defined as gastric or duodenal ulcer (GU or DU), and its complications are defined as either bleeding or perforation. Other rare complications such as obstruction are not considered in this study. Articles were found using the following terms: peptic ulcer, stomach ulcer, gastric ulcer, duodenal ulcer, gastroduodenal ulcer, peptic ulcer hemorrhage/bleeding, gastrointestinal hemorrhage/bleeding, peptic ulcer perforation, gastrointestinal perforation, or PUD complication, in conjunction with incidence or epidemiology. The search was restricted to human studies. We did not consider estimates published solely in letter, commentary, or abstract. Abstracts of all the entries retrieved by this strategy plus the references of selected original articles and some reviews related to PUD were examined to identify studies that satisfy the following predefined inclusion criteria: first, studies must have evaluated the general population. Randomized controlled trials typically included selected patient populations and were unlikely to provide generalizable estimates of the incidence; they were thus excluded. Second, study end points were PUD with or without complications. Third, studies were required to have reported or provided enough data for us to calculate the IR and its standard error.

Data extraction

Two investigators (Lin and Hernández-Díaz) recorded the data from selected publications independently. Decisions regarding inclusion of studies and data extraction were reached by consensus. We extracted IRs reported in the original articles or raw data for IR calculation together with information on study methods and objective quality-related characteristics. Variables assessed included the following: (1) basic demographics: geographic region, study years, mean age and female percentage of the study population; (2) methodological quality-related factors: prospective versus retrospective design, sample size (in terms of number of cases ascertained and the size of study population), method of estimating population at risk (the denominator of the incidence rate calculation, e.g., calculated based on a cohort in a claims database versus estimated by the demographic statistics of a catchment area), disease definition and specificity of the outcome definition (e.g., uncomplicated, complicated versus unspecified), source of cases (e.g., from clinical records, registries, electronic medical records, claims databases, etc.), exclusion criteria (e.g., cancer, esophageal varices, Mallory–Weiss disease, etc.), inclusion of hospitalized cases only, and validation of diagnosis by chart review.

Data analysis

Incident rates for each individual study were calculated by dividing the number of cases by the total number of person-years of follow-up. If the IRs of upper gastrointesctinal tract bleeding (UGIB) were reported, we would have included the estimates only if the percentage of bleeding caused specifically by peptic ulcer was provided by the same study, which allows the calculation of the incidence of peptic ulcer bleeding (PUB). Some studies divided their study population into nonsteroidal anti-inflammatory drug (NSAID) users and non-users, and reported incidence of PUD for the two cohorts separately. To get the estimates for the general population in such studies, we standardized the IRs according to the proportion of NSAID users in the study population. If one study presented estimates for more than one disease definition, all of them were considered. If multiple calendar time-specific IRs for a population were reported, all of them were considered because calendar time is also a factor of interest. Nevertheless, if an IR for the same population over the same period of time was reported in more than one article, only the most recent publication was included.

Log IRs of PUD with corresponding standard errors and random effect models were applied to calculate pooled IRs and 95% confidence intervals (CI).[8,9] Heterogeneity of effect estimates was assessed by using the Cochrane Q-test for heterogeneity.[10] Random effects meta-regressions were performed to identify study characteristics independently influencing IR estimates. Because some of the IRs were extracted from the same studies (i.e., the same population) for different calendar years, we used a generalized linear model to account for the correlation between observations. We built a

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separate meta-regression model for each disease definition and included only significant variables in each model, given limited number of selected articles within levels of outcome definition.

In a secondary analysis, to assess the effect of age and gender on PUD incidence, age and gender-specific IRs were extracted if a study provided such information. Because the data of person–time or number of cases are necessary for pooled analysis and calculation of relative risks and their variance across age or gender groups, age or gender-specific person–time was either collected from the original study or estimated by multiplying the total person–time by the age and gender distribution of the country where the study was conducted. The latter information was based on the demographic statistics from the United Nations.[11] Because different studies used different cut-points to categorize their population into age groups, we extracted the age-specific IRs from each study, assigned the mean age of the corresponding age group to the IRs, re-grouped all the age-specific IRs by the same a priori cut-points (<40, 40–70, and >70 years), and derived pooled estimates for each group.

We explored potential publication bias using both Begg's and Egger's test.[12–14] Stata 10.1 (Stata Corp., College Station, TX) was used for pooling the IRs and SAS 9.2 (SAS Institute Inc., Cary, NC) for meta-regression models. All the reported *p*-values were based on two-sided tests.

RESULTS

We identified 2890 relevant titles from PubMed and 2522 from EMBASE, and discarded 632 duplicates. After screening the titles, 395 abstracts and 119 complete articles were reviewed, and 88 were selected for detailed evaluation. Of these, 59 were rejected for the reasons as follows: the study population was not a general population or the IRs were reported for NSAID users and non-users, but no data were provided for estimating incidence among the general population ($n = 15$);[15–29] the outcome was UGIB, but the percentage of bleeding cases caused specifically by peptic ulcer was not provided ($n = 5$);[30–34] the same population was used by different studies ($n = 11$),[35–45] and only the most recent one is included; no IR estimates, person–time, or number of cases were available ($n = 13$);[6,46–57] the measure of frequency was prevalence rather than incidence ($n = 4$);[58–61] only mortality or operation rate was reported ($n = 9$);[62–70] and the outcome was DU or GU alone ($n = 1$).[71] We excluded another study because it used a rough approximation of population at risk (denominator); moreover, it was the only eligible article from a non-Western country.[72] By examining the references of all selected studies, we found two additional articles.[73,74] Therefore, the final number of studies for the main analysis was 31[2–5,44,75–99] (Figure 1). Table 1 summarizes the basic characteristics of the primary studies. Out of the 31 selected studies, we extracted 59 IRs because nine studies reported multiple IRs for different disease definitions or for different calendar years. We summarize in the following section several factors that significantly influence the IR estimates.

Disease definition

We categorized individual IRs into the following outcomes: uncomplicated PUD (UCPUD, $n = 10$), peptic ulcer bleeding (PUB, $n = 21$), perforated peptic ulcer (PPU, $n = 16$), peptic ulcer with bleeding or perforations ($n = 1$), and either mixed complicated and uncomplicated or not specified PUD (PUDNOS, $n = 11$). Because bleeding comprises the majority of PUD complications,[26,87,92] we incorporated the study investigating PUD with bleeding or perforations into the PUB category in our analysis ($n = 22$).

The pooled IR estimate per 1000 person-years was 0.90 (95%CI 0.78–1.04) for UCPUD, 0.57 (0.49–0.65) for PUB, 0.10 (0.08–0.13) for PPU, and 3.18 (2.05–4.92) for PUDNOS. We thereby calculated summary estimates only within levels of disease definition. Forest plots are presented in Figure 2.

Based on studies reporting both the incidence of UGIB and the percentage of PUB,[73,79,88–90,92,96,99] PUB comprised 39–62% of all the causes of UGIB; the pooled estimate per 1000 person-years was 1.12 (0.82–1.53) for UGIB and 0.48 (0.37–0.63) for PUB. Besides PUB, other common causes of UGIB included cancer, esophageal varices/ulcer, Mallory–Weiss disease, esophagitis, etc. In addition, five studies were excluded because they presented the incidence of UGIB without providing percentage of PUB;[30–34] they gave a pooled estimate of 1.04 (0.51–2.10) per 1000 person-years for UGIB, which is similar to the results from included studies.

Based on 22 included studies providing IRs of PUD by sites of the ulcer[3–5,74,75,78,79,81–85,87,88,90–93,95,96,98,99] and one additional study reporting only incidence for GU[71] the pooled IR estimate per 1000 person-years was 0.44 (0.35–0.54) for uncomplicated GU, 0.51 (0.38–0.67) for uncomplicated DU, 0.19 (0.15–0.23) for GU bleeding, 0.24 (0.19–0.30) for DU bleeding, 0.014 (0.008–0.024) for perforated GU, and 0.055 (0.038–0.079) for perforated DU.

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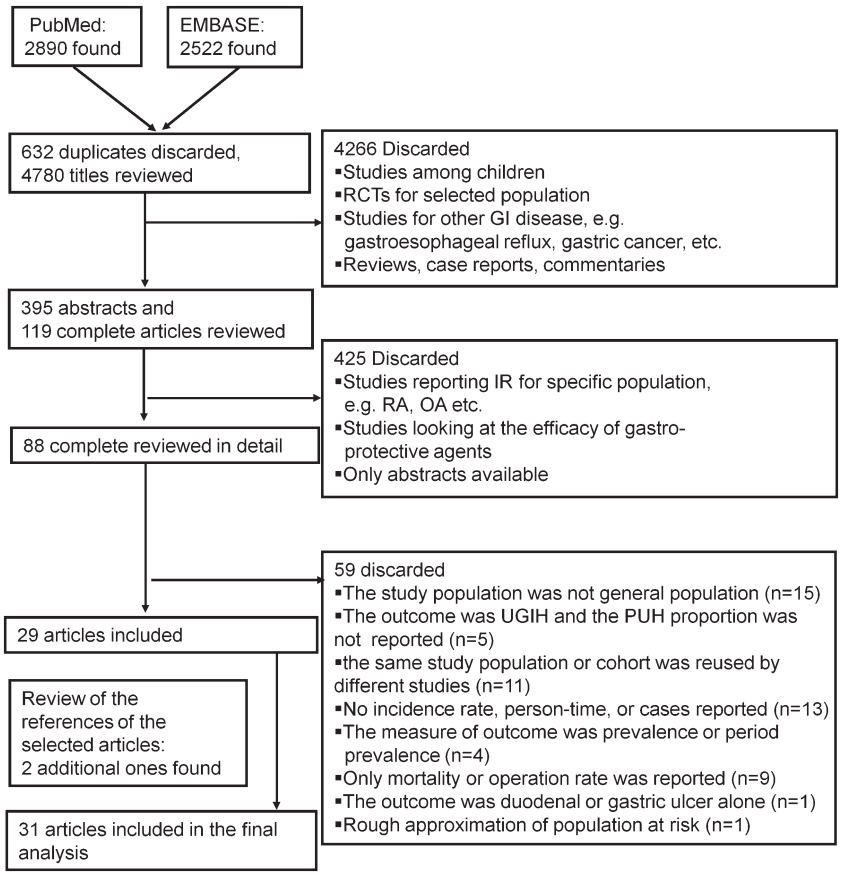

Figure 1. Flow chart of literature search for the studies reporting incidence of peptic ulcer disease

The IRs within categories of disease definitions were significantly heterogeneous. Note that the heterogeneity was larger for broad disease definitions, such as PUDNOS, than for specific ones, such as PUB (Figure 2). Further stratification and meta-regression were applied to explore sources of heterogeneity within each level of disease definition. Several factors were identified and are presented below.

Calendar year

For UCPUD, pooled estimates stratified by calendar year reveal a decreasing trend over time, with IRs per 1000 person-years being 1.41 (1.27–1.56) before 1985 and 0.80 (0.63–1.00) after 1995 (p-value for the difference <0.001). The trend is also observed for PUDNOS, but it was not significant for PUD complications (Table 2). Decreasing incidence of UCPUD and PUDNOS over time was reported within individual studies.[5,78,87] Some studies have also reported declining trends in the incidence of PUD complications.[5,75,100]

Hospitalized cases

Including only hospitalized cases was significantly associated with lower IRs for UCPUD ($p<0.0001$). The pooled IR of UCPUD was 0.71 (0.61–0.82) per 1000 person-years for studies including only admitted cases and 1.00 (0.85–1.17) for those without this restriction. This association between restriction to hospitalizations and IR magnitude was not, however, observed for PUD complications (Table 2).

Validation of cases

Validation of diagnosis by reviewing medical charts was significantly associated with smaller IRs, particularly for PPU and PUDNOS. Two studies validated a subsample of cases but did not reduce their estimates according to the positive predictive value.[77,87] We incorporated the two studies with those without validation. Our analysis showed that case validation may reduce the IR estimates by 49% (0–75%) for PPU and 45% (35–52%) for PUDNOS (Table 2).

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Table 1. Characteristics of the studies reporting incidence of peptic ulcer disease

First author	Geography	Disease definition[a]	Population at risk[b]	Source of cases[c]	Validation of cases[d]	Hospitalized cases only[e]	Exclusion criteria[f]	Age	person-year x1000	Mean study-year
Hermansson[75]	Sweden	PPU	Estimated	Clinical data	All	Yes	None	>20	3883[g]	1983
Bloom[3]	Pennsylvania, US	PUD	Cohort	Claims	None	No	Yes	Mean: 42.5	10	1985
Kurata[4]	Los Angeles, California, US	PUD	Estimated	Clinical data	All	No	None	>15	406	1979
Pérez-Aisa[5]	Zaragoza, Spain	PUB, PPU, UCPUD	Estimated	Clinical data	All	No	None	All age	1211[g]	1994
Czernichow[73]	France	PUB	Estimated	Clinical data	All	No	Post hoc	>18	1463	1996
Collier[74]	Cambridge, UK	PPU	Estimated	Clinical data	All	Yes	None	All	3000	1978
Menniti-Ippolito[76]	Umbria, Italy	CPUD, UCPUD	Cohort	Registry	All	Yes	Yes	35-84	189	1994
Jick[2]	Seattle, US	PPU	Cohort	Registry	All	Yes	Yes	>10	1595	1980
Andersen[77]	Copenhagen area, Denmark	PUB, PPU	Cohort	Registry	Some	Yes	None	20-93	354	1984
Bartholomeeusen[78]	Flanders, Belgium	PUD	Cohort	EMR	None	No	None	All age	255[g]	1999
Blatchford[79]	Scotland	PUB	Estimated	Clinical data	All	Yes	Post hoc	>15	1094	1993
Cutler[80]	USA	PUB	Estimated	Registry	None	Yes	Yes	All age	213084	1978
Eriksen[81]	Finnmark, Norway	PUD	Estimated	Clinical data	All	No	Yes	>16	37	1984
Everhart[82]	USA	PUD	Estimated	Interview	None	No	None	>18	38	1989
García Rodríguez[83]	United Kingdom	UCPUD	Cohort	EMR	All	No	Yes	40-79	1167	1997
Johnsen[84]	Northern Norway	PUD	Cohort	Clinical data	All	No	None	20-49	127	1983
Kiaer[85]	Faroe island, Denmark	PUD	Estimated	Clinical data	All	No	None	>15	97	1982
Lanza[86]	USA	PUD	Cohort	Claims	All	No	Yes	20-64	24	1990
Lassen[87]	Funen, Denmark	UCPUD, PUB, PPU	Cohort	Registry	Some	No	Yes	All age	965[g]	1998
Longstreth[88]	San diego, USA	PUB	Cohort	Claims	All	Yes	Post hoc	>20	271	1991
MacDonald[89]	Tayside, Scotland, UK	UCPUD, PUB, PPU	Cohort	Registry	All	Yes	Post hoc	>50	376	1990
Masson[90]	Scotland	PUB	Estimated	Clinical data	All	Yes	Post hoc	All age	938	1992
Ohmann[91]	Dusseldorf, Germany	PUB	Estimated	Clinical data	All	No	Yes	All age	1143[g]	1995
Rockall[92]	England	PUB	Estimated	Clinical data	All	Yes	Post hoc	>16	4063	1993
Rosenstock[93]	Denmark	PUD	Cohort	Interview/ registry	All	No	Yes	30-60	26	1988
Smalley[94]	Tennessee, USA	PUD	Cohort	Claims	All	Yes	Yes	>65	162	1985
Soplepmann[95]	Estonia	PUB	Estimated	Clinical data	All	Yes	Yes	>15	252	1993
Soplepmann[96]	Central Finland	PUB	Estimated	Clinical data	All	Yes	Post hoc	>15	436	1993
Svanes[97]	Western Norway	PPU	Estimated	Clinical data	All	Yes	Yes	20-90	13120	1963
Taha[98]	Southwest Scotland	PPU	Estimated	Clinical data	All	No	None	All age	2554	2002
Leerdam[99]	Amsterdam, Netherlands	PUB	Estimated	Clinical data	All	Yes	Post hoc	All age	3179[g]	1997

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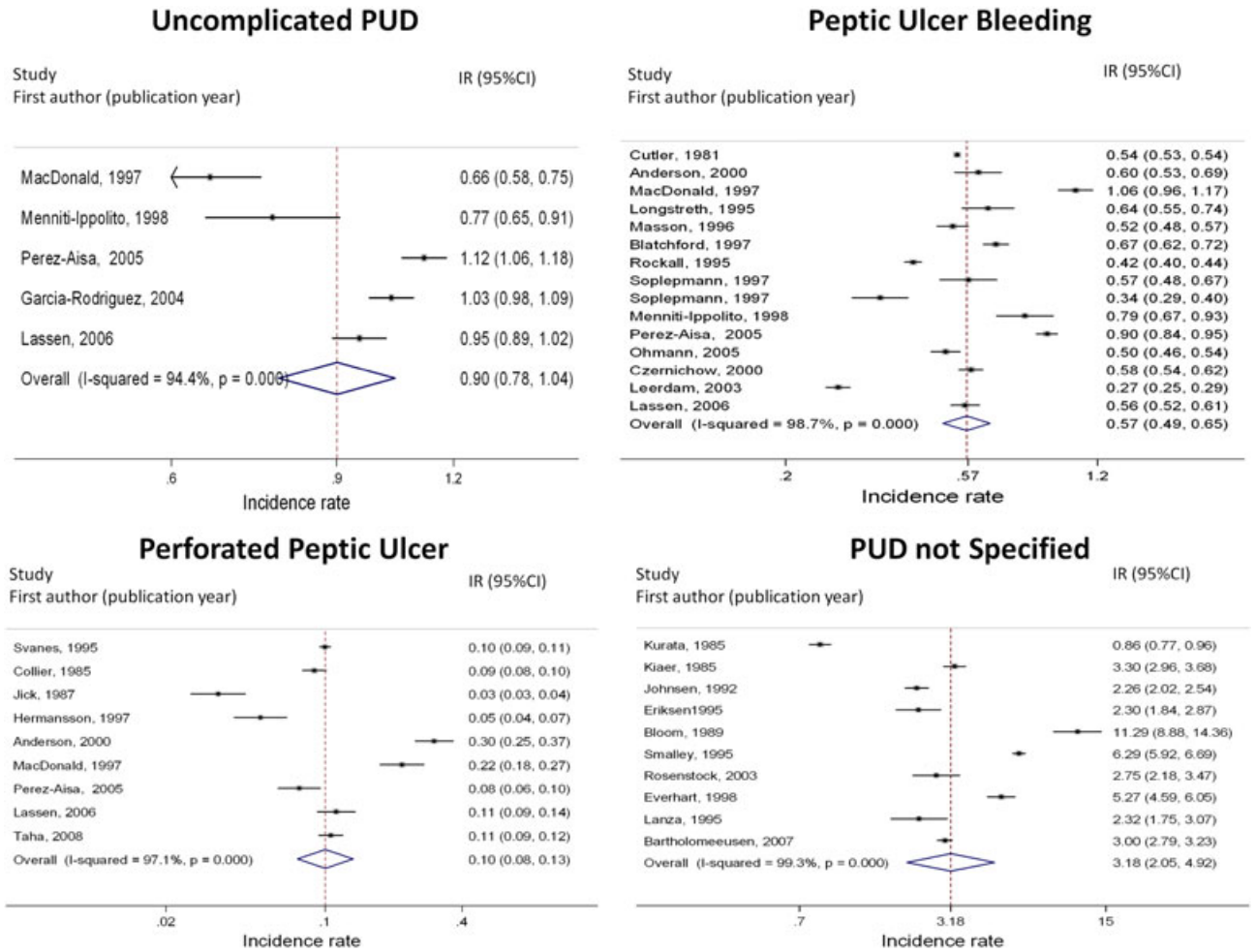

Figure 2. Forest Plots by disease definition PUD, peptic ulcer disease, IR: incidence rate. Note: If a study reported multiple IR estimates for the same outcome [e.g., based on different time periods], we pooled them first by inverse-variance weights. Therefore, on the plots there is only one incident rate estimate per study

Source of cases

Eighteen studies identified the cases directly from the clinic or hospital (Table 1). Compared with studies using administrative claims or registries, such studies tended to report smaller IRs for PUB ($p = 0.042$) and PUDNOS ($p < 0.001$). The observed effect remained significant after adjusting for validation in the multivariate meta-regression models. Among the 25 studies that validated cases, the pooled PUDNOS IR per 1000 person-years was 2.09 (95%CI 1.19–3.68,

[a]UCPUD, uncomplicated PUD; PUB: peptic ulcer bleeding; PPU, perforated peptic ulcer; PUD, PUD not specified or any PUD, grouped as PUDNOS in the subsequent analyses; CPUD, complicated PUD, including hemorrhagic and perforated peptic ulcers; PUD, peptic ulcer disease.
[b]Cohort = primarily defined study population in which the cases were identified; estimated, ascertainment of case series followed by secondary estimation of the person–time in the source population that gave rise to these cases.
[c]The source where the cases were found: Clinical data: hospital/clinic records; Registry: hospital discharge or disease registries; EMR, electronic medical record; Claims: Claims administrative database; interview: cases identified through interview/questionnaire.
[d]The ascertainment of the cases involved not only computerized codes but also other information (e.g., medical records) to confirm the diagnosis. None. no validation; some, validating a subsample of cases but using non-validated cases as well; all, using only validated cases.
[e]Including only hospitalized cases.
[f]Using certain exclusion criteria when selecting the cases (e.g. cancer, esophageal varices, Mallory–Weiss disease, alcoholism, chronic liver disease, etc.). Yes, the author applied certain exclusion criteria; Post hoc, the author-reported incident rate of upper gastrointestinal bleeding, the exclusion of other causes was achieved by reducing the incident rate according to the proportion of PUB provided by the investigators.
[g]The original paper reported different incidence rates for different calendar year. In this table is the sum of all person–time.

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Table 2. Study characteristics affecting incident rate estimates

Outcome category[a]	Characteristics	Categories	No.[b]	Pooled estimates	Meta-regression [c]	
					Incidence rate ratio	*p*-value
UCPUD	–		10	**0.90(0.78-1.04)[d]**	0.28(0.19-0.42)	<0.0001
PUB			22	**0.57(0.49-0.65)[d]**	0.18(0.12-0.29)	<0.0001
PPU			16	**0.10(0.08-0.13)[d]**	0.03(0.02-0.04)	<0.0001
PUDNOS			11	**3.18(2.05-4.92)[d]**	1	Ref
UCPUD	Calendar year	<=1985	1	**1.41(1.27-1.56)[d]**	1.83(1.63-2.06)	<0.001
		1985-1995	5	**0.97(0.76-1.24)[d]**	1.49(1.19-1.87)	<0.001
		>1995	4	**0.80(0.63-1.00)[d]**	1	Ref
	Hospitalized cases only	No	8	**1.00(0.85-1.17)[d]**	1	<0.001
		Yes	2	**0.71(0.61-0.82)[d]**	0.53(0.43-0.66)	
PUB	Case identified by clinical data	No	7	0.66(0.54-0.81)	1	0.042
		Yes	15	0.56(0.46-0.68)	0.74 (0.55-0.99)	
	Hospitalized cases only	No	10	0.69(0.58-0.81)	1	0.34
		Yes	12	0.51(0.44-0.61)	0.88(0.69-1.14)	
PPU	Validation of cases	No	3	0.15(0.07-0.33)	1	0.064
		Yes	13	0.08(0.06-0.1)	0.51 (0.25-1.04)	
PUDNOS	Calendar year	<=1985	6	3.18(1.55-6.54)	6.08(5.63-6.57)	<0.001
		1985-1995	4	**3.47(2.58-4.68)[d]**	2.45(2.08-2.89)	<0.001
		>1995	1	**1.86(1.65-2.10)[d]**	1	Ref
	Validation of cases	No	4	4.55(2.53-8.17)	1	<0.001
		Yes	7	2.49(1.33-4.68)	0.55(0.48-0.65)	
	Case identified by clinical data	No	7	4.05(2.71-6.04)	1	<0.001
		Yes	4	1.96(1.02-3.78)	0.41(0.33-0.51)	

Note: The *p*-values for heterogeneity[10] were below 0.001 for all the strata with more than 1 estimate except the stratum with hospitalized cases only for UCPUD ($n=2$), which had a *p*-value of 0.145.

[a]PUD, peptic ulcer disease; UCPUD, uncomplicated PUD; PUB, peptic ulcer bleeding; PPU, perforated peptic ulcer; PUDNOS, PUD not specified.

[b]Number of estimates within the strata.

[c]Meta-regression models built within strata of disease definition; results were adjusted for all the other significant variables in the strata.

[d]The 95% confidence intervals do not overlap with one another across joint strata by the study characteristic and disease definitions.

$n=18$) for those identifying cases directly through clinical data and 3.86 (95%CI 1.45–10.27, $n=7$) for those using other sources such as claims or electronic medical records, both of which were lower compared with that for those without validation of cases (IR 4.55, 95%CI 2.53–8.17).

Age

Among the 31 selected articles, 15 provided age-specific IRs[2,5,74,78–80,84,88,89,91,95,96,98,99] of PUD. Although age is strongly associated with IRs of PUD in general, it might affect specific PUDs differentially. When the population was categorized by a priori age cut-points (<40. 40–70, and >70 years), the pooled IR in the oldest group was 13.3 (7.3–24.5) times that in the youngest for PUB, but it was 4.9 (3.0–8.2) times for UCPUD. Overall, the increasing IR trend reached plateau for UCPUD in the middle ages whereas the curve kept growing exponentially for complicated PUD with age. Not surprisingly, studies that restricted the sample to elderly patients reported higher incidences.[89,94]

Gender

The 10 studies providing gender-specific IRs of PUD reported lower IRs for females.[2,4,5,80,81,84,85,91,94,95] The difference between males and females was more prominent in the past than in more recent years, particularly for uncomplicated PUD. For instance, the pooled RR for males versus females dropped from 2.0 (1.6–2.5) before 1995 to 1.3 (1.0–1.8) after 1995 for UCPUD. In contrast, the RR for gender difference only changed from 2.4 (1.9–3.1) before 1995 to 2.0 (1.1–3.6) after 1995 for PUB.

Publication bias

No evidence of publication bias was found within levels of disease definition. Take UCPUD for example. The *p*-values from Begg's and Egger's tests were 0.18 and 0.26, respectively. Similarly, all the tests for small study effects were non-significant for other disease definitions.

Sensitivity analysis

We evaluated the influence of individual studies by omitting one study at a time. Overall, no single influential study was identified: all the pooled estimates after omitting each of the studies fell within the 95 %CI of the primary pooled estimates.

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DISCUSSION

In the general population, the pooled IR estimates per 1000 person-years were 0.90 for UCPUD, 0.57 for PUB, 0.10 for PPU, and 3.18 for PUDNOS. Aside from calendar year, distribution of age, and gender of the study population, several methodological characteristics of the study were also found to significantly affect the estimation of PUD incidence; these factors include validation of cases, source of the cases, and specificity of the outcome definition.

Validation of cases was associated with a smaller IR of PUD, particularly for PPU and PUDNOS. According to prior studies, the positive predictive value of PUD cases identified solely based on computerized codes was 69–73% for UCPUD and 73–93% for PUB.[77,87,101] It is therefore important to consider the validity of case ascertainment methods when estimating the IR of both complicated and uncomplicated PUD.[102] Identification of cases directly from a clinic or hospital source rather than from computerized health care databases, was associated with lower IRs for PUB and PUDNOS independently of case-validation.

Including only cases admitted to a hospital was associated with smaller IR estimates. This criterion might reduce the number of false positives (e.g., gastrointestinal symptoms erroneously coded as PUD in claims databases). However, this restriction may miss real cases, perhaps those milder and treated in an outpatient setting, and therefore, underestimate IRs in particular for uncomplicated PUD.[103] Czernichow *et al.* estimated that 16% of all patients with UGIB were treated as out-patients [73]. This percentage is believed to be higher for UCPUD.[104]

One third of included studies did not differentiate specific PUD outcomes and we categorized them as investigating PUDNOS. On average, studies reporting IR of PUDNOS had smaller sample size in terms of total number of cases (mean 328, 95%CI 135–521) compared with those looking at PUB (mean 562, 95%CI 332–792) or UCPUD (mean 752, 95%CI 287–1218). Those PUDNOS studies may be underpowered to divide their cases according to finely defined definitions. Besides, compared with the studies differentiating uncomplicated versus complicated PUD, less PUDNOS studies validated their cases. Our analysis showed that case validation may reduce the IR estimates of PUDNOS by 45% (35–52%). Taken together, with smaller number of unvalidated cases, studies reporting PUDNOS tend to report unstably high incidence of PUD. Given the variety of clinical presentations of PUD, it may not be informative to report estimates without distinguishing, at least, complicated from uncomplicated PUD.

As had been shown before, IRs declined with calendar year, particularly for uncomplicated PUD.[5–7] The decreasing *Helicobacter pylori* infection prevalence may partly account for the decreasing incidence of uncomplicated PUD.[105,106] The increase in the utilization of gastro-protective agents and coxibs could have also contributed to this trend.[5,7,50,78,107] On the other hand, the aging of the population over time[92] and the widespread use of NSAIDs and aspirin, especially among the elderly[91] could have slowed down the decline in UCPUD, and might explain the apparently steady incidence of complicated PUD over time. For PUD overall, a steeper decline has been observed for males than for females[4,5,75]. As a result, while male gender has been a consistent risk factor for PUD, there is evidence of diminishing gender difference over time.[81]

Old age has been associated with higher incidence of both uncomplicated and complicated PUD. However, while the incidence of UCPUD reached plateau in the middle age, the IR estimates for PUB kept growing exponentially with age. This supports a different manifestation of PUD by age groups, with the elderly having a disproportionally higher odd of complications than the youth.[5,54,87,89]

Among the four studies reporting IRs of both UCPUD and PUB,[5,76,87,89] the pooled IR per 1000 person-years was 0.86 (0.70–1.06) for UCPUD and 0.81 (0.61–1.07) for PUB, which could translate into an estimated percentage of PUB among all PUDs of 48.5%. This percentage was 61.6 % for the study including only individuals more than 50 years old[89] and 43.5% for the other studies using the general adult population.[5,76,87] The proportion of PUB among all PUDs is likely to be determined by the age of the population and the calendar time because our results suggest that the incidence of UCPUD significantly decreased over time and that of PUB did not.

We need to acknowledge several limitations. Only if the studies are combinable can meta-analyses be justified to integrate results of independent studies. However, this can be quite a strong assumption when dealing with observational studies based on heterogeneous populations. Indeed, heterogeneity was found even within levels of disease definition and finely stratified analysis by other study characteristics is limited by the number of selected studies. Besides, some eligible articles might have escaped our attention in spite of our attempt of a thorough search. To avoid selective oversights of studies reporting extreme estimates, the decisions regarding inclusion or exclusion of a study had been made independently of their results. It is reassuring that our sensitivity analysis by excluding studies one at a time

did not identify any influential study. Finally, all the study populations came from Western countries, and results might not be generalizable to non-Western populations.

In summary, the IR per 1000 persons per year is around 1.0 for uncomplicated and 0.7 for complicated PUD in the general population. Studies restricted to hospitalized cases, using only validated cases, or identifying cases directly from clinical data tended to report smaller IR estimates for PUD. Comparisons of IR estimates need to take into account disease definition and other study characteristics.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- In the general population, the incidence of uncomplicated PUD is in the order of 1 case per 1000 person-years; and the incidence of PUD complications is 0.7 cases per 1000 person-years.
- Disease definition, restriction to hospitalized cases, case validation, case ascertainment source, and calendar time affected the PUD IR estimate significantly.
- The incidence of PUD, particularly of uncomplicated PUD, has declined over the last decade.

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