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Statin Intake and Gastric Cancer Risk: An Updated Subgroup Meta-analysis Considering Immortal Time Bias

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A retrospective record-linkage study (RLS) based on medical records containing drug prescription histories involves immortal time bias (ITB). Thus, it is necessary to control for this bias in the research planning and analysis stages. Furthermore, a summary of a meta-analysis including RLSs that did not control for ITB showed that specific drugs had a preventive effect on the occurrence of the disease. Previous meta-analytic results of three systematic reviews evaluating the association between statin intake and gastric cancer risk showed that the summary hazard ratio (sHR) of the RLSs was lower than 1 and was statistically significant. We should consider the possibility of ITB in the sHR of RLSs and interpret the results carefully.

Key words: Data linkage, Bias, Hydroxymethylglutaryl-CoA reductase inhibitors, Stomach neoplasms, Meta-analysis

Pharmacoepidemiology studies can be categorized by their design as retrospective record-linkage studies (RLSs) based on medical records containing drug prescription histories, and prospective post-hoc analyses of randomized controlled trials (PRTs) [1,2]. However, RLSs applying secondary data involve immortal time bias (ITB); thus, it is necessary to control for this bias in the research planning and analysis stages [3]. A study participant must survive the period between entry into the cohort and the first prescription of the medication being evaluated in order to receive the medicines for incident-free follow-ups [4]. The ITB systematically underestimates the incidence rate in the group exposed to the medication; thus, a RLS might conclude that the drug prevents the outcome analyzed in the study [5]. Furthermore, a summary of a meta-analysis including RLS studies that did not control for ITB showed that specific drugs had a preventive effect on the occurrence of the disease.

While approximately 50% of gastric cancers may be triggered by several risk factors [6], there is increasing interest in chemoprevention against gastric cancer based on the preventive effect of eradicating *Helicobacter pylori* [7]. Liu et al. [8] reported that simvastatin inhibited gastric cancer cells by suppressing RhoA activity, and den Hoed and Kuipers [9] suggested that statin intake may lead to a modest reduction of gastric cancer risk.

The author searched PubMed for relevant articles published through May 2, 2022. Table 1 summarizes the meta-analytic results of 3 systematic reviews evaluating the association between statin intake and gastric cancer risk [10-12]. The summary hazard ratio (sHR) of the RLSs was lower than 1 and was statistically significant [11,12]. However, the selected PRT articles differed between the 2 studies [10,11], with the sHR showing conflicting results. For a more scientifically rigorous interpretation, an updated subgroup meta-analysis [13,14] of 8 articles [15-22] included in the 3 systematic reviews is presented in Table 1. Although there were 3 papers published using the same cohort (the Korean National Health Insurance Service cohort) through the search date [18,23,24], the study of You et

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al. [18], with the longest follow-up period, was selected as a representative. A forest plot illustrated that the sHR of the 4 RLSs [15-18] showed a consistent preventive effect, whereas that of the 4 PRTs [19-22] did not (Figure 1).

Several methods including matching, analysis using time-dependent covariates, and the difference of cumulative incidence, have been suggested to control for ITB [3,25]. Cheung et al. [17] conducted a sensitivity analysis to control for ITB by treating all medications, including statins, as time-varying covariates in a multivariable Cox model. However, any RLS should consider other time-related biases, including protopathic bias, latency time bias, time-window bias, immeasurable time bias, and depletion of susceptibility, in addition to ITB [3].

Therefore, the possibility of ITB in the sHR of RLSs should be considered. It would be more appropriate to deduce that there is no association between statin intake and gastric cancer risk based on PRTs, because PRTs enable a more scientifically valid interpretation of the data than RLSs. Furthermore, Hippisley-Cox and Coupland [20] reported a difference in the hazard ratio between men and women (Figure 1); therefore, the effect of statin intake according to sex should be evaluated in future studies.

Table 1. Summary hazard ratios (sHRs) and their confidence intervals (CIs) of the published systematic reviews

Study	Searching	Selected	sHR (95% CI)	I-squared (%)
Singh et al. 2013 [10]	Dec 2012	3 PRT	0.83 (0.66, 1.05)	-
Wu et al. 2013 [11]	Mar 2013	3 PRT	0.73 (0.53, 0.93)	28.5
		3 RLS	0.87 (0.77, 0.99)	24.7
Seo et al. 2022 [12]	2020	5 RLS	0.71 (0.59, 0.85)	68.0

PRT, post-hoc analysis of a randomized controlled trial; RLS, record-linkage study.

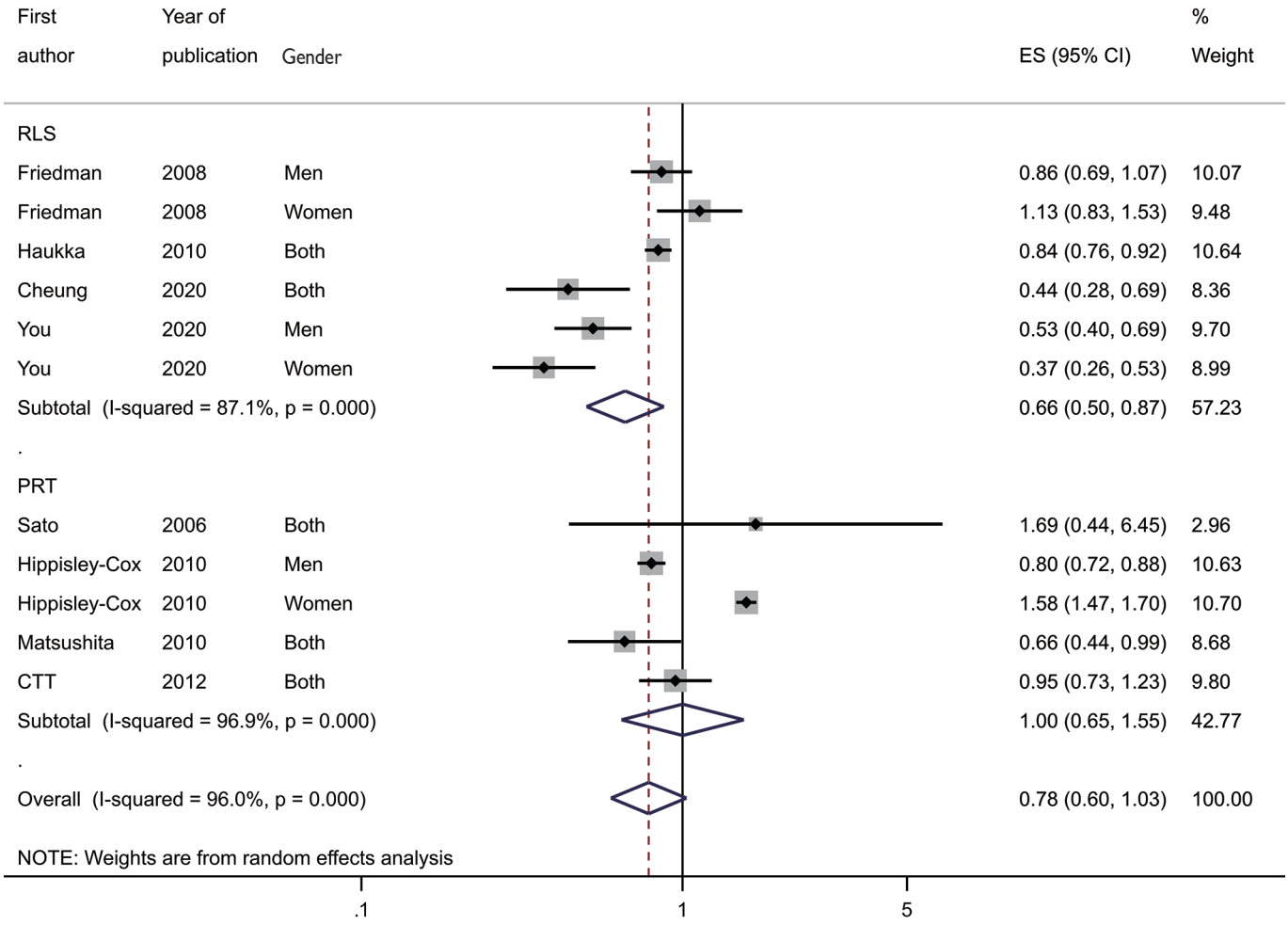

Figure 1. Forest plot by study design. RLS, record-linkage study; PRT, post-hoc analysis of a randomized trial; ES, effect size ; CI, confidence interval.

Ethics Statement

This study was waived by an ethics review board because the study subjects were published articles.

CONFLICT OF INTEREST

The author has no conflicts of interest associated with the material presented in this paper.

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