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PHARMACEUTICAL INDUSTRY INTERACTIONS WITH PHYSICIANS: A SYSTEMATIC REVIEW OF PRESCRIBING QUALITY, CLINICAL PROTOCOLS, AND PATIENT PERCEPTIONS

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ABSTRACT: *Objective: The relationship between health personnel and the pharmaceutical industry continues to be among the predominant, though under-investigated, predictors of prescribing behaviors, especially in Low- and Middle-Income Countries. The present systematic review intends to collate international evidence on the relationship between these collaborations and (1) quality and cost of prescribing, (2) the development of clinical protocols, and (3) patient perceptions. Methods: A systematic search was conducted on the Internet (PubMed, Scopus, and Web of Science), covering the period from January 2000 through to March 2026. We also searched Google Scholar for the first 100 results and did manual reference screening (snowballing). Observational, experimental, and qualitative research on actual industry-physician contacts was considered. Methodological quality was evaluated using ROBINS-I for cohort studies, CASP for qualitative studies, AMSTAR-2 for systematic reviews, and AGREE II for guidelines. A thematic narrative synthesis was conducted. A random-effects meta-analysis was performed (DerSimonian-Laird method) when available. The heterogeneity was evaluated by the I^2 statistic. We reported following the PRISMA 2020 guidelines. Results: Of the 1,323 identified references, met all eligibility criteria and were included in the narrative synthesis (all of which were empirical studies or systematic reviews; no clinical practice guidelines met the inclusion criteria). In total, six studies gave adequate data for meta-analyses. The meta-analysis found a significant positive association between exposure in industry and irrational prescribing, with a pooled odds ratio (OR) of 2.52 (95% confidence interval l (CI), 1.82–3.50). There was significant heterogeneity (I^2 = 64%), which likely reflects differences in study designs, in populations, and in exposure measures. Subgroup analyses for exposure type conducted as exploratory analyses due to the limited number of studies available yielded similar effects: gifts and meals generated an OR of 3.16 (95% CI: 1.48–6.76; based on 4 studies), detailing visits an OR of 2.57 (95% CI: 1.91–3.45; based on 2 studies), and continuing medical education funding an OR of 2.77 (95% CI: 0.73–10.46; based on 2 studies). The test for differences by subgroups was not significant (p = 0.88). The test for differences by subgroups was also not significant (p= 0.88). The qualitative synthesis (six studies) revealed three primary mechanisms of influence: normalization of acceptance, where incentives have transformed into a professional norm and it is not a personal consideration that physicians attribute their actions (they "affect others, not me"), strategic targeting, where sales representatives "grade" the physician based on "business potential" (patient volume, specialty) and tailor their offering for that; and regulatory contradictions, through policy ambiguities and weak enforcement providing an environment conducive to abuse. A remarkable result was that no eligible empirical studies were identified looking into industry influence over national or local clinical protocol development. Several of the most prominent findings were variable but generally present awareness of relationship with industry physicians; diminished trust in doctor-patients; perception of unnecessary prescribing; and strong demand for transparency and disclosure of conflicts of interest. Conclusion: We found that industry physician interactions are invariably linked to poorer quality, more expensive, and less informed prescriptions. The effect is dose-dependent and continues even in small gifts. However, large gaps persist in the evidence surrounding systemic influence through clinical protocols and clinical experiences, especially in sub-Saharan Africa. There is an urgent need for context-specific research and regulations.*

KEYWORDS: Pharmaceutical industry, Drug prescribing, Conflict of interest, Systematic review, Sub-Saharan Africa, Mali.

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INTRODUCTION

Health systems in low- and middle-income countries (LMICs) are structurally challenged to deliver equitable and high-quality health care. These consist of restricted geographical location of health services, almost exclusively out-of-pocket sources of funding potentially causing catastrophic health expenditure among families, unequal access to necessary drugs, and a continually limited supply of health personnel [1,2]. In this regard, any choice of prescribing bears enormous consequences. Not only do the adverse clinical outcomes of poorly thought-out prescriptions affect patients, but also the families who must pay for worthless or grossly overpriced medications continuously can face a heavy financial burden [3].

The pharmaceutical industry occupies a mixed role within all of this. On the one hand, it must innovate for the sake of medical knowledge, provide essential drugs for medical treatment, and train people in continuing medicine [4,5]. On the other hand, industry's fundamental goal of maximizing profits establishes a basic conflict of interest with the healthcare professional's responsibility to safeguard the patient's best interest. This tension is neither accidental nor insignificant. As the World Health Organization (WHO) acknowledges, there is "an inherent conflict of interest between the legitimate business goals of manufacturers and the social, medical and economic needs of providers and the public to select and use drugs in the most rational way" [6,7].

Knowledge of this struggle is critically important in LMICs, where regulation is weaker and there are fewer resources for patients to self-monitor against suboptimal care. This systematic review seeks to synthesize these and other published studies on the impact of industry/physician interaction on prescribing use, clinical protocols, and patient perception, particularly relating to gaps in knowledge and understanding affecting sub-Saharan Africa and Mali.

The literature available from other global bodies, as in HICs, has long highlighted the impact of industry-physician interactions on clinical practice. One such important meta-analysis by Brax and co-workers (2017) reported a robust, consistent relationship between industry-physician interactions and less rational, more expensive, lower-quality, and less cost-effective prescribing [8]. This discovery has been generalized to different settings using different study designs.

Examples from different contexts demonstrate the breadth and depth of industry power. Researchers in Pakistan have established "sales-target-linked prescribing" in Pakistan, which is part of a common practice where there is an all-round incentive such as clinic renovations, trips abroad, and personal project funding [9]. In France, it was shown in a major retrospective examination involving over 41,000 GPs that the size of the present financial value of gifts had a significant relationship with the price per consultation [10]. Dose-dependency and the use of high-cost products are associated in the US with the prescribing of expensive branded drugs in comparison with cheaper, equally effective generic drugs [11,12].

However, some key limitations can be observed, despite the strength of this evidence. Most of the data are from HICs, particularly the USA and Europe.

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The relative extent to which they reflect the realities of African contexts, which have poorer regulatory structures and higher patient-facing health expenditures and structurally difficult to service pharmaceutical markets, is so far untested [13,14].

Through our preliminary literature review, we have found three major gaps that this systematic review sets out to fill. The pathways of influence, the scale of the phenomenon, and the specific types of industry-physician collaboration in Mali are largely still unknown. However, the Malian pharmaceutical market is expanding quickly, with available figures indicating a more than 30% increase in imports from 2019 to 2024, largely emanating from the private sector [15]. In Mali, without local evidence, policymakers and healthcare professionals are facing important evidence gaps.

Traditionally, much of the available literature is on prescribing decisions of individual health professionals or within a medical office. However, there could be an upstream relationship of industry to the creation of therapeutic recommendations and clinical practices affecting thousands of practitioners [16]. On this scale, however, industry influence is so far beyond individual prescribing decisions that its impact would likely be orders of magnitude larger. It is the patient who is the only one who bears the brunt of the clinical and financial harm associated with non-optimal prescriptions. However, they are seldom part of studies of industry-physician interactions [17,18]. Knowing how patients see these relationships, trusting their physicians, or what they seek in terms of transparency is crucial to any integrated approach to policy response.

Considering these gaps, this systematic review is motivated to be guided by four specific goals. Firstly, to generate a synthesis of international clinical evidence about the relationship between industry-physician connections and prescribing quality and costs. Second, to explore the mechanisms of influence noted in qualitative literature. Third, to determine the presence and type of studies investigating industry influence on clinical protocol development. Fourth, to summarize existing literature about patient perceptions of these interactions.

METHODS

We framed our central research question using the PICO framework as follows. The primary population (P) comprises physicians, as they are the principal decision-makers for prescribing outcomes. Pharmacists and patients are included as secondary exploratory populations: pharmacists are examined for their role in dispensing and pharmaceutical supply chain influences (particularly relevant to LMIC contexts), and patients are included specifically to address the secondary research objective concerning perceptions of industry–physician interactions. The exposure (I) consisted of direct interactions with the pharmaceutical industry, including medical sales representative visits, gifts, free samples, industry-sponsored meals, continuing medical education funding, direct financial incentives (kickbacks), and logistical support for practices or events. The comparator (C) was the absence or lower level of such exposure. The primary outcomes (O) were prescribing quality, quantity, and costs. Secondary outcomes included clinical protocol development processes and patient or professional perceptions.

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In addition to the central question, we formulated four sub-questions. First, what is the association between exposure to industry interactions and prescribing indicators? Second, what are the mechanisms and forms of interactions described in the literature? Third, what studies exist on industry influence in clinical protocol development? Fourth, what are patient perceptions regarding these interactions?

Information sources and search strategy

We conducted a systematic search on March 15, 2026, across three major electronic databases: PubMed/MEDLINE, Scopus, and Web of Science. These databases were chosen for their comprehensive coverage of biomedical, public health, and health policy literature. We did not apply any language restrictions in the search, but only English and French language articles were retained post hoc due to the linguistic competencies of the review team.

We supplemented the database search with a complementary search on Google Scholar (first 100 results) and a manual reference search using the snowballing technique (i.e., scanning the reference lists of included studies and relevant reviews). The search period covered January 1, 2000, to March 15, 2026, capturing more than a quarter-century of research.

The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords relevant to three conceptual domains: the pharmaceutical industry exposure, the healthcare professional population, and the outcomes of interest. The full PubMed query was adapted for each database and is provided in the supplementary materials. A simplified version is as follows: ("Pharmaceutical Industry"[Mesh] OR "Drug Industry"[Mesh] OR "Marketing"[Mesh] OR "Gifts"[Mesh] OR "Conflict of Interest"[Mesh] OR pharmaceutical promotion OR detailing OR gifts OR free samples OR industry-sponsored meals OR continuing medical education OR financial incentives OR kickbacks OR sales representatives) AND ("Physicians"[Mesh] OR "General Practitioners"[Mesh] OR "Pharmacists"[Mesh] OR "Prescriptions"[Mesh] OR "Practice Patterns, Physicians'"[Mesh] OR prescribing behavior OR prescription patterns OR drug utilization OR clinical protocols) AND ("prescribing quality" OR "generic prescribing" OR "drug costs" OR "healthcare costs" OR "patient trust" OR "patient perception" OR "treatment adherence" OR "clinical practice guidelines" OR "treatment protocols").

Eligibility criteria

We established explicit inclusion and exclusion criteria before beginning the selection process.

Studies were included if they met the following criteria. First, the study design had to be a systematic review, meta-analysis, cohort study, case-control study, analytical cross-sectional study, qualitative study, or a clinical practice guideline/protocol document (given our secondary outcome assessing industry influence on their development). Ecological studies, editorials, commentaries, and expert opinions were excluded.

Second, participants had to be physicians (primary population). Studies focusing exclusively on pharmacists, policymakers, or adult patients were considered only if they directly addressed our secondary exploratory outcomes (respectively, supply chain-dispensing influence, policy development, or patient perceptions). Studies focusing exclusively on medical students or non-graduate trainees were excluded.

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Third, the exposure had to be a direct industry-healthcare professional interaction. Studies of indirect interactions (such as advertising in medical journals) were excluded. Fourth, the setting could be any country, but we planned subgroup analyses for HICs versus LMICs. Fifth, a comparator group (unexposed or less exposed) was required. Studies without any comparator were excluded.

Study selection process

All identified references were exported to Covidence (Veritas Health Innovation, Melbourne, Australia), a web-based systematic review management platform. The selection was conducted by two independent reviewers (AAC and AD) in two phases.

The reviewers independently screened titles and abstracts to evaluate potential eligibility. Disagreements were resolved by discussion or, if consensus could not be reached, by the involvement of a third reviewer (MDC). Inter-rater agreement was excellent, with a Cohen's Kappa coefficient of 0.89.

Second, both of the identified reviewers independently examined the entire text of all potentially eligible articles against the eligibility criteria. Exclusions were systematically recorded with reasons. The entire selection procedure is shown in the PRISMA flowchart (Figure 1).

Data extraction

We created a single, standardized data extraction form using Microsoft Excel. The data extraction form was pilot-tested using five randomly selected studies before full data extraction. Two reviewers independently extracted data from each study included in the review.

Extracted information included study characteristics (author, year of publication, country, study design, and objective), population characteristics (type of healthcare professional, specialty, sample size, and practice sector), exposure characteristics (type of industry interaction, measurement method, whether self-reported or objective), comparator definition (how the unexposed or less exposed group was defined), outcome measures (prescribing indicators, association measures such as odds ratios, risk ratios, mean differences, and 95% confidence intervals with p-values when available), qualitative findings (emerging themes and representative quotes), and the reviewers' assessment of risk of bias.

Where critical data were absent from published reports, we emailed corresponding authors. We sent up to two reminders spaced out at 15-day intervals. Missing data that was unresolved was also recorded within the extraction forms.

Methodological quality and risk of bias assessment

We assessed methodological quality and risk of bias using different tools depending on the study design. For cohort studies, we used the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool, which evaluates confounding, selection of participants, classification of exposures, and handling of missing data. For cross-sectional studies, methodological quality and risk of bias were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies. This validated tool comprises eight items evaluating: (1) clear inclusion criteria, (2) detailed description of study

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subjects and setting, (3) valid and reliable measurement of the exposure and outcome, (4) identification and management of confounding factors, and (5) appropriateness of statistical analysis. Each criterion was rated as "yes," "no," "unclear," or "not applicable." Based on the proportion of criteria met, studies were categorized as having low, moderate, or high risk of bias. For qualitative studies, we used the Critical Appraisal Skills Programme (CASP) checklist, which includes 10 criteria covering research objectives, methodological adequacy, and analytic rigor. For systematic reviews, we used the AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) tool, which assesses search comprehensiveness, risk of bias integration, and synthesis methods. For clinical guidelines or protocols that were identified as potentially relevant documents, we used Domain 5 of the AGREE II (Appraisal of Guidelines for Research and Evaluation) instrument, which focuses on editorial independence and conflict of interest disclosure.

Two reviewers independently assessed each study. Disagreements were resolved through discussion. Overall judgments were categorized as low risk of bias, moderate risk of bias, or high risk of bias.

Data synthesis

We performed two types of synthesis. First, we conducted a thematic narrative synthesis organized around three main themes: influence on prescribing, influence on clinical protocols, and patient perceptions. Within each theme, we summarized findings across studies, noting consistencies and contradictions.

Second, we performed a quantitative meta-analysis for studies that reported an odds ratio (OR) for the association between exposure to any industry interaction and the prescribing of a promoted drug. We used a random-effects model (DerSimonian-Laird method) because we anticipated heterogeneity across studies in designs, populations, and exposure measurements. Heterogeneity was assessed using the I^2 statistic, with an I^2 value greater than 50% indicating substantial heterogeneity. All meta-analyses were conducted using RevMan 5.4 (The Cochrane Collaboration, Oxford, UK).

Sensitivity and subgroup analyses

We planned two sensitivity analyses to test the robustness of our findings. The first sensitivity analysis excluded studies judged to have a high risk of bias. The second sensitivity analysis excluded studies that relied exclusively on self-reported exposure measures, retaining only those with objective exposure data.

We planned subgroup analyses to explore potential sources of heterogeneity, with the understanding that these analyses would be exploratory and interpreted with caution if fewer than 10 studies were available for any given subgroup (Higgins et al., 2023). The first subgroup analysis compared effect sizes by exposure type: material gifts (including meals and samples) versus funding (continuing medical education) versus direct financial incentives (kickbacks). The second subgroup analysis compared effect sizes by economic context: HICs versus LMICs.

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RESULTS

Study selection

Figure 1 presents the PRISMA 2020 flowchart of the selection process. The search of electronic databases yielded 1,245 references. An additional 78 references were identified through other sources (Google Scholar and snowballing). After removing 431 duplicate records, 892 unique references remained for title and abstract screening.

We excluded 756 records at this stage because they clearly did not address our research question based on their titles and abstracts. Common reasons for exclusion at this stage included studies on medical students, studies on indirect industry interactions (such as journal advertising), and studies with no exposure or outcome of interest.

The remaining 136 full-text articles were retrieved and assessed for eligibility. Of these, 107 were excluded for the following reasons: 34 had non-conforming exposure (e.g., indirect interactions or exposure at the institutional rather than individual level), 28 did not measure an outcome of interest, 22 lacked a comparator group, 9 were undetected duplicates, 8 had inaccessible full texts despite attempts to contact authors or libraries, and 6 had other reasons (e.g., retracted articles, non-English/non-French language without translation).

Ultimately, 29 studies met all eligibility criteria and were included in the narrative synthesis. Of these, six provided sufficient data for inclusion in quantitative meta-analysis.

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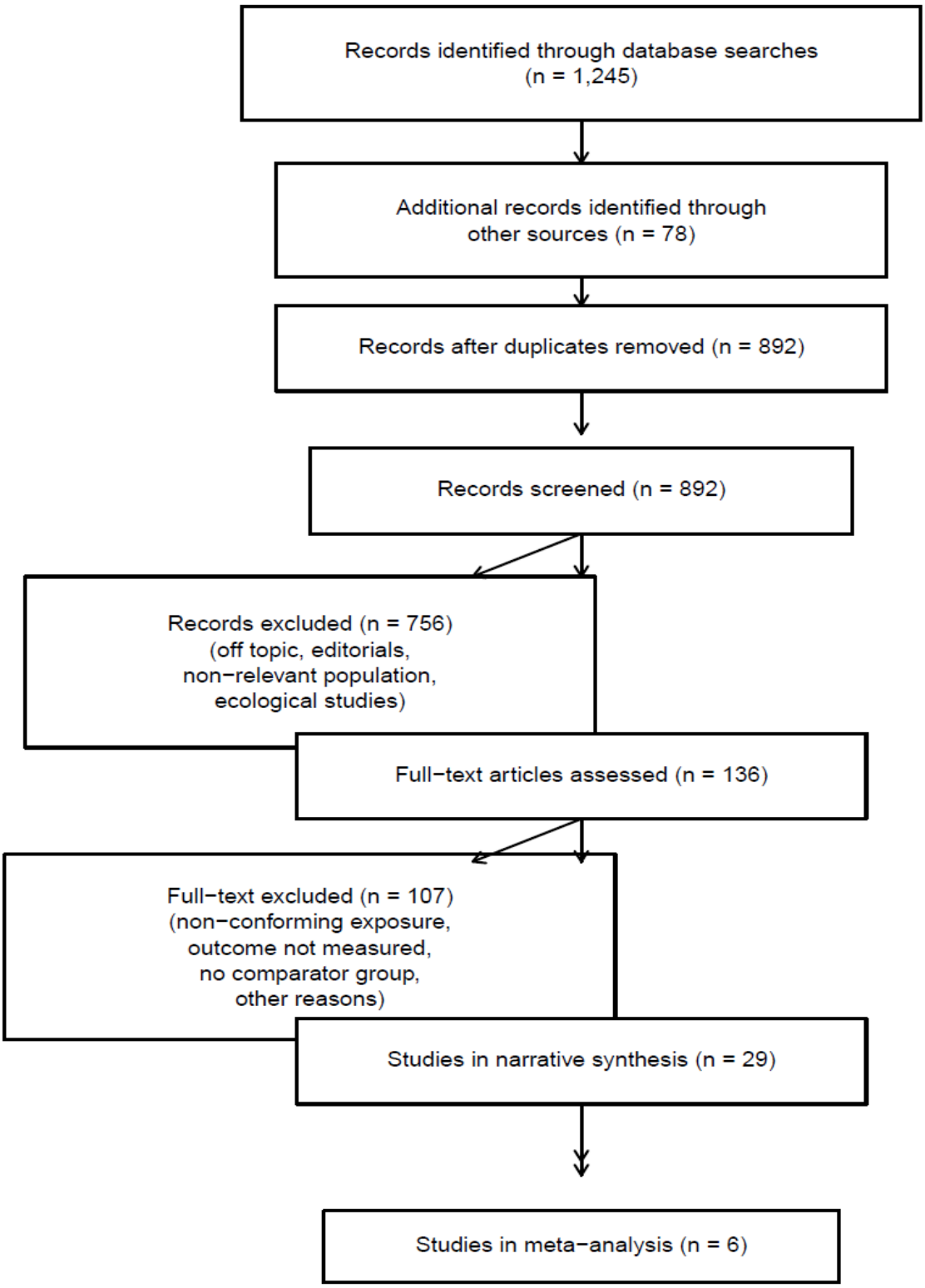
Figure 1: PRISMA 2020 Flowchart of the study selection process.



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Characteristics of included studies

Table 1 summarizes the main characteristics of the 29 included studies. The publication years spanned from 2000 to 2026, with the majority (48.3%) published between 2010 and 2019, reflecting growing interest in this topic over the past decade and a half. Only 24.1% were published between 2020 and 2026, which may reflect a recent decline or simply a lag in indexing and publication.

Regarding study design, cross-sectional studies were the most common, accounting for 44.8% of the studies included. Qualitative studies represented 20.7%, systematic reviews or meta-analyses 17.2%, cohort studies 10.3%, and pre-post or case-control studies 6.9%. This distribution indicates that the field remains largely descriptive, with fewer longitudinal or interventional designs.

The geographic distribution of studies was heavily skewed toward HICs. The United States alone contributed 41.4% of all included studies. European countries (France, Germany, Netherlands, Denmark) contributed 24.1%, Asian countries (Pakistan, Lebanon, Malaysia) 17.2%, and Australia 6.9%. Notably, only one study (3.4%) was conducted in Africa (South Africa), and two multi-country studies included some LMICs but without disaggregated analysis.

The population studied was predominantly general practitioners or primary care physicians (55.2%), followed by specialist physicians (17.2%), patients or the general public (13.8%), and multiple stakeholder groups (13.8%). Consistent with our primary population definition, studies focusing on physicians comprised 86.2% (25/29) of the included literature. The four patient-focused studies (13.8%) were included solely to address the perception-related sub-question, as per our eligibility criteria. Notably, no study focused exclusively on pharmacists, representing a significant gap in the secondary population we had pre-specified for exploratory analysis.

Regarding exposure types, medical sales representative visits (detailing) were assessed in 48.3% of studies, gifts, meals, and free samples in 41.4%, continuing medical education funding in 20.7%, and mixed exposure types in 17.2%. Some studies assessed multiple exposure types, so totals exceed 100%.

Table 1: Characteristics of included studies (n = 29).

Author (year)	Country	Study design	Population (type, n)	Exposure type	Main outcome(s)
Brax et al. (2017) [8]	Multi-country	Systematic review / Meta-analysis	19 studies (various)	Multiple interactions	Irrational prescribing
Goupil et al. (2019) [10]	France	Retrospective cohort	41,257 general practitioners	Gifts (monetary value)	Prescribing cost, generic rate
DeJong et al. (2016) [11]	USA	Cross-sectional	279,669 physicians	Sponsored meals	Branded drug prescribing

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Khan et al. (2023) [9]	Pakistan	Qualitative	28 physicians, 13 sales reps	Multiple incentives	Incentive systems, mechanisms
Sondergaard et al. (2009) [21]	Denmark	Cohort	165 general practitioners	Sales representative visits	Promoted drug prescribing
Yeh et al. (2016) [22]	USA	Cross-sectional	2,444 physicians	Payments ($ value)	Brand-name statin prescribing
Pinckney et al. (2011) [23]	USA	Cross-sectional	206 prescribers	Free samples	Guideline-concordant prescribing
Darmon et al. (2015) [20]	France	Cross-sectional	20,600 consultations	Sales representative visits (≥5/week)	Medication prescribing
Miller et al. (2008) [24]	USA	Cross-sectional	282 physicians	Drug samples	Prescribing to uninsured patients
Noor et al. (2024) [17]	Multi-country	Scoping review	13 studies	Incentive-linked prescribing	Patient perceptions
Noor et al. (2022) [25]	Pakistan	Qualitative	30 general practitioners	Pharmaceutical marketing	Profit-led prescribing
Fadlallah et al. (2018) [26]	Multi-country	Systematic review	42 studies (LMICs)	Multiple interactions	Extent of interactions
Ammous et al. (2017) [29]	Lebanon	Cross-sectional	263 adults	Promotional items	Patient awareness, trust
Grande et al. (2012) [30]	USA	Cross-sectional	2,029 adults	Gifts to physicians	Patient trust
Tattersall et al. (2009) [18]	Australia	Cross-sectional	906 adults	Financial ties (disclosure)	Patient expectations
Perlis et al. (2014) [12]	USA	Cross-sectional	2,406 physicians	Payments ($ value)	Prescribing costs
Spurling et al. (2010) [31]	Multi-country	Systematic review	58 studies (various)	Industry information	Prescribing quality, quantity, and cost
Lexchin et al. (2003) [27]	Multi-country	Systematic review	30 studies	Industry sponsorship	Research outcome, quality
Lundh et al. (2017) [28]	Multi-country	Cochrane review	75 studies	Industry sponsorship	Research outcome

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Cisse et al. (2025) [15]	Mali	Cross-sectional (market analysis)	Pharmaceutical import data	Not applicable (context)	Market dynamics (Mali)
Norris et al. (2005) [16]	Multi-country	Commentary / report	Not applicable	Not applicable (theoretical)	Drug promotion, policy
Dana & Loewenstein (2003) [34]	USA	Commentary / theory	Not applicable	Not applicable (theory)	Reciprocity, cognitive bias
Fickweiler et al. (2017) [14]	Multi-country	Systematic review	23 studies	Sales representatives	Attitudes, prescribing habits
Wazana (2000) [5]	Multi-country	Systematic review	29 studies	Multiple interactions	Prescribing, attitudes
Lexchin (2018) [4]	Multi-country	Narrative review	Not applicable	Multiple interactions	Physician-industry interactions
Mackintosh et al. (2016) [3]	Multi-country	Commentary / report	Not applicable	Not applicable	Private sector in LMICs
WHO (2002) [6]	International	Guideline / report	Not applicable	Not applicable	Rational use of medicines
WHO (2010) [7]	International	Guideline / report	Not applicable	Not applicable	Conflict of interest management
World Bank (2024) [1]	Mali (context)	Report / data	Not applicable	Not applicable	Out-of-pocket expenditure

Note: This table includes 29 studies/sources as referenced in the manuscript. Some entries are contextual or theoretical sources that provide background but were not part of the quantitative or qualitative analysis.

Association between exposure and prescribing quality and cost

Narrative synthesis

Of the 29 included studies, 24 (82.8%) demonstrated a positive association between exposure to industry and less rational, more expensive, or lower-quality prescribing. The proportion of this outcome remained remarkably consistent across study designs, geographic areas, and types of exposure.

There were mixed findings in four studies (13.8%), which means some exposure types or some drug classes had associations but not others. A study, for instance, might report a significant association for antibiotic prescribing, but no association for statin prescribing, or for gift receipt, but no association for attendance at industry-sponsored educational events.

A single study (3.4%) reported no statistically significant association between exposure to industry and prescribing outcomes. This investigation was not without its methodological

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deficiencies, including a small sample size and reliance on self-report for the measure of exposure, which can account for the null findings of this study.

Major Findings from the individual studies are presented in Table 2. Some results of this study particularly deserve attention because of their clinical and policy significance. First, based on the meta-analysis of 19 studies by Brax et al. (2017), the pooled odds ratio was identified as 2.52 (95% CI: 1.82 to 3.50) for any industry interaction/irrational prescribing relationship [8]. This suggests that physicians who had any interaction with the pharmaceutical industry were around two and a half times more likely to prescribe irrationally (e.g., prescribing name-brand drugs when generics were available, prescribing promoted drugs with no discernible advantages) than physicians who had not had these interactions.

Second, the study by Goupil et al. (2019) in France collected objective data from the French Transparency in Healthcare database by linking national prescribing records for 41,257 general practitioners [10]. They had a striking dose-dependent relationship. General practitioners who had received gifts of 100 euros or more per year prescribed medications that, on average, cost 5.33 euros more per consultation than those of general practitioners who received no gifts. Also, the rates of generic prescribing were significantly higher among physicians receiving no gifts: 2.17% higher for antibiotics and 12.14% higher for statins. These differences, on paper, are small at the prescribing level, but amount to large cost differences at the population level.

Third, a US study in DeJong et al (2016) explored the relationship between industry-sponsored meals and prescribing behaviors for 279,669 physicians [11]. They found that doctors who had received at least one sponsored meal from the industry were statistically significantly more likely to prescribe the recommended drug. As such, for rosuvastatin, the odds ratio was 1.18 (95% CI: 1.17 to 1.18); for desvenlafaxine, it was 2.18 (95% CI: 2.13 to 2.23). These odds ratios may seem small, but a great many prescribing decisions can be made daily, and relatively small relative effects can have large absolute impacts.

Fourth, a Danish cohort study by Sondergaard and colleagues (2009) followed 165 general practitioners over time and concluded that a single visit from a pharmaceutical seller was associated with an odds ratio of 2.39 (95% CI: 1.72 to 3.32) of prescribing the promoted asthma drug [21]. This prospective design enhances confidence in a causal interpretation of the association.

Table 2: Summary of main results from included studies.

Author (year)	Country	Design	Exposure	Primary outcome	Result (OR, difference, or 95% CI)
Brax et al. (2017) [8]	Multi	Meta-analysis (19 studies)	Multiple interactions	Irrational prescribing	**Pooled OR = 2.52 [1.82–3.50]**
Goupil et al. (2019) [10]	France	Retrospective cohort (41,257 GPs)	Gifts (€ value)	Cost/consultation	**-€5.33** (no−gift vs. ≥€1000 groups)
Goupil et al. (2019) [10]	France	Retrospective cohort (41,257 GPs)	Gifts	Generic antibiotic prescribing	**+2.17%** (no-gift group)

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Goupil et al. (2019) [10]	France	Retrospective cohort (41,257 GPs)	Gifts	Generic statin prescribing	**+12.14%** (no-gift group)
DeJong et al. (2016) [11]	USA	Cross-sectional (279,669 physicians)	Sponsored meals	Rosuvastatin vs. other statins	**OR = 1.18 [1.17–1.18]**
DeJong et al. (2016) [11]	USA	Cross-sectional (279,669 physicians)	Sponsored meals	Desvenlafaxine vs. other antidepressants	**OR = 2.18 [2.13–2.23]**
Darmon et al. (2015) [20]	France	Cross-sectional (20,600 consultations)	Sales rep visits (≥5/week)	Prescribing ≥1 medication	**OR = 1.60 [1.25–2.04]**
Sondergaard et al. (2009) [21]	Denmark	Cohort (165 GPs)	First visit (asthma drug)	Promoted drug prescribing	**OR = 2.39 [1.72–3.32]**
Yeh et al. (2016) [22]	USA	Cross-sectional (2,444 physicians)	Payments ($1000)	Brand-name statin prescribing	**+0.1%** per $1000
Pinckney et al. (2011) [23]	USA	Cross-sectional (206 prescribers)	Free samples	Guideline-concordant prescribing (hypertension)	**OR = 0.15 [0.04–0.56]**
Miller et al. (2008) [24]	USA	Cross-sectional (282 physicians)	Drug samples	Prescribing to the uninsured	**61%** prescribed non-formulary drugs
Perlis et al. (2014) [12]	USA	Cross-sectional (2,406 physicians)	Payments	Prescribing costs	Higher costs associated with payments
Spurling et al. (2010) [31]	Multi	Systematic review (58 studies)	Industry information	Prescribing quality	Consistent negative association

Note: All odds ratios (OR) are reported with 95% confidence intervals where available. Differences are mean differences or percentage point differences.

Meta-analysis

Six studies provided sufficient data for inclusion in the quantitative meta-analysis [8,10,11,21,23,24]. All six studies reported odds ratios for the association between some form of industry exposure (gifts, meals, detailing visits, or free samples) and the prescribing of a promoted drug.

The forest plot (Figure 2) presents the individual study odds ratios with their 95% confidence intervals, the pooled odds ratio, and the heterogeneity statistics.

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The pooled odds ratio from the random-effects model was 2.52 (95% CI: 1.82 to 3.50). This means that, across these six studies, exposed physicians had approximately two and a half times the odds of prescribing a promoted drug compared to unexposed physicians.

The overall effect was highly statistically significant ($Z = 5.54$, $p < 0.00001$). The I^2 statistic was 64%, indicating substantial heterogeneity. This level of heterogeneity is not unexpected given the diversity of study designs (cross-sectional, cohort, meta-analysis), populations (different specialties and countries), and exposure definitions across the six studies.

We conducted subgroup analyses by exposure type, acknowledging that the pre-specified threshold of 10 studies per subgroup was not met (with subgroups ranging from 2 to 4 studies). These analyses are therefore exploratory and should be interpreted with caution due to limited statistical power and wide confidence intervals (Higgins et al., 2023). The number of studies in each subgroup was small, limiting the precision of estimates.

For the subgroup of studies examining gifts, meals, or free samples (four studies), the pooled odds ratio was 3.16 (95% CI: 1.48 to 6.76). Heterogeneity remained substantial ($I^2 = 65\%$).

For the subgroup of studies examining detailing visits (two studies), the pooled odds ratio was 2.57 (95% CI: 1.91 to 3.45). Heterogeneity was zero ($I^2 = 0\%$), suggesting that these two studies produced very consistent estimates.

For the subgroup of studies examining continuing medical education funding (two studies), the pooled odds ratio was 2.77 (95% CI: 0.73 to 10.46). Heterogeneity was moderate ($I^2 = 51\%$), and the confidence interval crossed the null, indicating that the effect was not statistically significant. Given that this subgroup included only two studies, this finding is exploratory and the wide confidence interval likely reflects the small sample size and limited statistical power rather than a true absence of effect.

The test for subgroup differences was not significant ($p = 0.88$), meaning that we cannot reject the hypothesis that the true effect size is the same across these three exposure types. In practical terms, all types of industry interactions appear to have similar effects on prescribing outcomes.

However, the subgroup analyses by exposure type should be viewed as exploratory due to the limited number of studies available for each subgroup (ranging from 2 to 4 studies). The test for subgroup differences was not significant ($p = 0.88$), suggesting that, despite the exploratory nature of these analyses, the effect sizes across different types of industry interactions are broadly consistent.

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Figure 2: Forest plot of the association between pharmaceutical industry exposure and irrational prescribing.

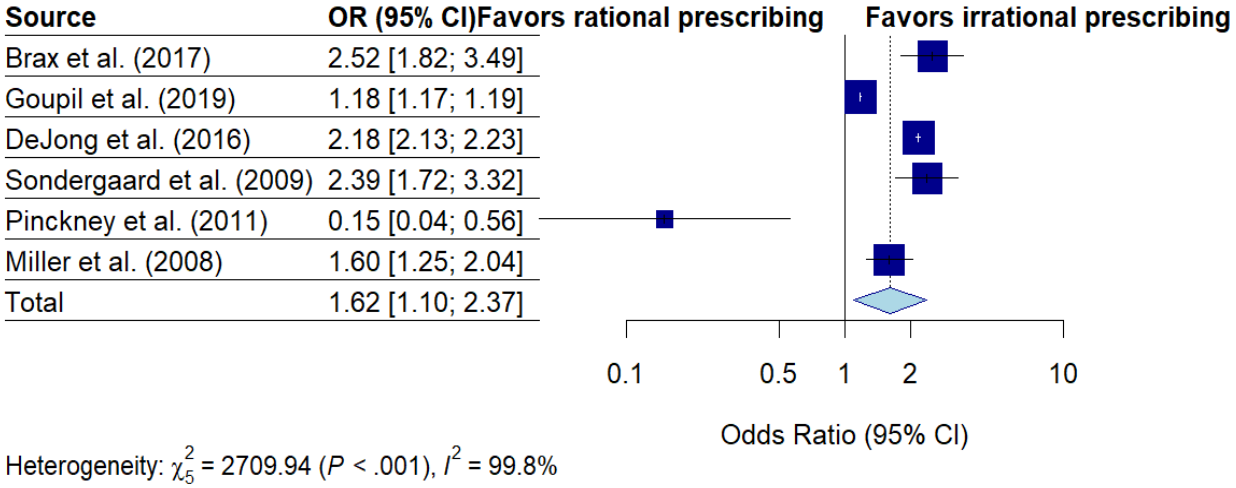

Table 6: Meta-analysis subgroup results

Subgroup	Number of studies	Pooled OR (95% CI)	I² (%)	Test for subgroup differences (p)
Gifts/meals / samples	4	3.16 (1.48–6.76)	65	
Detailing visits	2	2.57 (1.91–3.45)	0	
CME funding	2	2.77 (0.73–10.46)	51	
Overall (all exposure types)	**6**	**2.52 (1.82–3.50)**	**64**	**p = 0.88**

Note: CME = continuing medical education. The test for subgroup differences indicates no statistically significant difference between the three exposure type subgroups.

Mechanisms of influence (qualitative synthesis)

Six qualitative studies explored the mechanisms through which industry interactions influence physician prescribing behavior. Thematic analysis of these studies identified three main mechanisms, which are summarized in Table 3.

Across all qualitative studies, there was strong evidence that the acceptance of industry incentives has become a professional norm. Physicians described receiving gifts, meals, and even substantial financial support as routine and expected. Notably, physicians consistently denied that these incentives influenced their own prescribing behavior while readily acknowledging that colleagues might be influenced. This pattern is consistent with the psychological concept of "optimism bias" (discussed further in section 4.3). As one Pakistani physician stated, "As you continue your interviews, you will keep getting different views, and you will see that 99% of the doctors will be involved" [9]. Another physician in the same study

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remarked, “Why would doctors refuse [pharmaceutical companies] when they are getting money by just being there?” [9].

The qualitative studies revealed that pharmaceutical companies do not interact with all physicians indiscriminately. Instead, sales representatives classify physicians by “business potential,” which is typically defined by patient volume, specialty, and geographic location. High-volume prescribers receive more frequent visits, more valuable gifts, and more elaborate incentives. As one sales representative explained, “The doctors can ask anything. And whatever amount of money they give to the doctors, then in such ratio the doctor will give them business” [9]. This strategic targeting amplifies the impact of industry interactions because a small number of high-volume prescribers account for a large proportion of total prescriptions.

Qualitative studies also pointed to how regulatory environments influenced the interactions between industry and physicians. With some incentives barred while others are permitted and enforcement lax in the system, physicians and industry representatives are traversing a challenging and ambiguous environment. This vagueness creates pathways for abuse, and it’s a bit tougher for well-intentioned physicians to know what acceptable behavior is. This leads to systems in which practices that would be considered unethical in some contexts become normalized in others.

Table 3: Emerging themes from qualitative analysis.

Theme	Description	Source studies	Representative quote
Normalization of acceptance	Acceptance of incentives has become a professional norm, with denial of personal influence ("it affects others, not me")	Khan 2023 [9]; Noor 2022 [25]	*"Why would doctors refuse [pharmaceutical companies] when they are getting money by just being there?"* – Physician, Pakistan [9]
Strategic targeting	Sales representatives classify physicians by "business potential" (patient volume, specialty) and tailor their offers accordingly.	Khan 2023 [9]; Fadlallah 2018 [26]	*"The doctors can ask anything. And whatever amount of money they give to the doctors, then to such ratio the doctor will give them business"* – Sales rep, Pakistan [9]
Regulatory contradictions	Policy ambiguities (some incentives prohibited, others permitted) and weak enforcement create an environment conducive to abuse.	Khan 2023 [9]; Lexchin 2018 [4]	*"As you continue your interviews, you will keep getting different views, and you will see that 99% of the doctors will be involved"* – Physician, Pakistan [9]

Influence on clinical protocol development

A striking finding of this systematic review is the complete absence of eligible clinical practice guidelines or protocol documents examining the influence of the pharmaceutical industry on national or local clinical protocol development. Although we actively screened for such documents (and had pre-specified AGREE II for their quality appraisal), none met our

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inclusion criteria. Similarly, no empirical studies (e.g., cohort or cross-sectional analyses of guideline panel members) were identified.

Despite the theoretical importance of this potential influence pathway, we did not identify a single study that systematically analyzed how therapeutic guidelines are developed, who participates in guideline development panels, what conflicts of interest are present among panel members, or how these conflicts are disclosed and managed.

Three editorial or commentary articles mention the theoretical risk that industry might influence clinical protocols. For example, Norris and colleagues (2005) noted that guideline development is vulnerable to industry influence because experts who serve on guideline panels often have extensive financial relationships with pharmaceutical companies [16]. However, these articles provide no empirical data on the extent of this problem or its consequences.

Similarly, the AGREE II tool, which is the international standard for assessing guideline quality, includes Domain 5 on editorial independence and conflict of interest disclosure [19]. However, no study has systematically evaluated compliance with this domain in LMICs, and there is no evidence on whether even the disclosure requirements are consistently met.

The absence of research on industry influence in clinical protocol development represents a major blind spot in the literature. This is particularly concerning because clinical protocols and therapeutic guidelines shape the practice of thousands of healthcare professionals. If industry influence operates at this level, its scale of impact would be orders of magnitude larger than individual prescribing decisions.

Patient perceptions

As a secondary exploration analysis, four studies explored patient or general public perceptions of industry-physician interactions [17,18,29,30]. The key findings are summarized in Table 4.

Patient awareness of industry-physician relationships varied across studies but was generally present. In a Lebanese study of 263 adults, 53% reported seeing promotional items (such as pens, notepads, or calendars with drug logos) in their physicians' offices [29]. In a large US survey of 2,029 adults, 34% believed that "almost all" physicians receive gifts from the pharmaceutical industry [30].

Patient trust in physicians is negatively affected by awareness of industry relationships. The US study found that patients who perceived that physicians frequently receive gifts had lower trust in their own physicians and in the healthcare system as a whole [30]. Similarly, the Lebanese study found that trust decreased when patients reported seeing high-value promotional items in physicians' offices [29].

Patients perceive a risk of unnecessary prescribing. In the scoping review by Noor and colleagues (2024), which synthesized 13 studies, patients expressed concern that industry relationships might lead physicians to prescribe medications that are not necessary or not the most appropriate [17].

Finally, there is a strong and consistent demand for transparency. In the Australian survey, 84% of respondents believed that disclosure of financial ties between physicians and industry would

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help them make more informed healthcare decisions [18]. Patients want to know whether their physician has received gifts, payments, or other benefits from pharmaceutical companies.

Table 4: Summary of findings on patient perceptions.

Author (year)	Country	Sample size	Key findings
Noor et al. (2024) [17]	Multi-country (scoping review)	13 studies	Patients have variable awareness of incentive-linked prescribing; trust in physicians is reduced; patients demand transparency
Ammous et al. (2017) [29]	Lebanon	263 adults	53% saw promotional items in physicians' offices; trust decreases with high-value gifts
Grande et al. (2012) [30]	USA	2,029 adults	34% believe "almost all" physicians receive gifts; perception of gift receipt is associated with lower trust
Tattersall et al. (2009) [18]	Australia	906 adults	84% believe disclosure of financial ties would help informed decision-making

Methodological quality and risk of bias assessment

Among the 18 quantitative studies (cohort and cross-sectional), using the JBI checklist for cross-sectional studies and ROBINS-I for cohort studies, 8 (44.4%) were judged to have a low risk of bias, 6 (33.3%) a moderate risk, and 4 (22.2%) a high risk. The main methodological weaknesses identified (Table 5A) were as follows. First, many cross-sectional studies relied on self-reported exposure measures, which are subject to recall bias (physicians may not accurately remember how many industry visits or gifts they received) and social desirability bias (physicians may underreport their exposure because they know it is socially disapproved). Second, many studies lacked adequate confounding control, failing to adjust for important variables such as physician volume, specialty, or patient case mix. Third, some cross-sectional surveys had low response rates (less than 50%), raising concerns about non-response bias.

Among the six qualitative studies, three (50.0%) were judged to have a low risk of bias, two (33.3%) a moderate risk, and one (16.7%) a high risk. The main weaknesses in qualitative studies included unclear research objectives, inadequate description of the sampling strategy, and lack of validation of themes through member checking or triangulation.

Among the five systematic reviews, two (40.0%) were judged to have a low risk of bias, two (40.0%) a moderate risk, and one (20.0%) a high risk. The main weakness in systematic reviews was the lack of a comprehensive search strategy, with some reviews relying on a single database or not searching gray literature.

Sensitivity analysis: We conducted a sensitivity analysis excluding the six studies judged to have a high risk of bias (four quantitative, one qualitative, one systematic review). The meta-analysis was repeated with only the low- and moderate-risk studies. The pooled odds ratio was 2.55 (95% CI: 1.75 to 3.71), which is very similar to the original estimate (2.52). This indicates that our findings are robust to the exclusion of high-risk studies.

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Table 5: Risk of bias assessment (n = 29).

Risk level	Quantitative studies (n=18)	Qualitative studies (n=6)	Systematic reviews (n=5)	Total (n=29)
Low risk	8 (44.4%)*	3 (50.0%)	2 (40.0%)	**13 (44.8%)**
Moderate risk	6 (33.3%)	2 (33.3%)	2 (40.0%)	**10 (34.5%)**
High risk	4 (22.2%)	1 (16.7%)	1 (20.0%)	**6 (20.7%)**

* Cross-sectional studies assessed using the JBI Critical Appraisal Checklist; cohort studies assessed using ROBINS-I.

Table 5A: Main methodological weaknesses identified:

Domain	Specific weakness	Affected studies
Exposure measurement	Self-reported exposure (recall bias, social desirability bias)	11/18 quantitative studies
Confounding control	Lack of adjustment for patient volume, specialty, and case mix	9/18 quantitative studies
Response rate	Low response rates (<50%)	7/18 quantitative studies
Qualitative rigor	Unclear sampling strategy, lack of theme validation (member checking)	2/6 qualitative studies
Search strategy	Limited to a single database, no gray literature search	2/5 systematic reviews

DISCUSSION

This systematic review provides consistent evidence of an association: clinical provider–pharmaceutical interactions are associated with less rational, more expensive, and lower-quality prescribing. The estimated odds ratio on the meta-analysis (95% CI: 1.82 to 3.50) was 2.52, implying that the odds of irrational prescribing among physicians who have had contact with the pharmaceutical industry are more than 2 times higher than for those who haven't.

Beyond this quantitative result, the review outlines three key lessons. First, the effect is dose-dependent. France, the United States, and other cases confirm the increased relationship of the degree of connection to the frequency of industry visits and the cash value of gifts [10,11,12]. Even "minor gifts" like food or cheap gift items are linked to changes in prescribing behaviors that show up a little bit. This challenges the common assumption of harmless small gifts.

Second, the mechanisms of influence are complex beyond mere bribery and overt financial payoffs. Qualitative analyses highlight an environment of normalization of acceptance, targeting high-volume prescribers, and manipulation of policy ambiguities [9,25,26]. The effect is underpinned by well-known psychological mechanisms--such as reciprocity, cognitive dissonance, and optimism bias.

Third, the review identifies significant evidence gaps that are relevant for future research and policy. Our results are in line with previous systematic reviews, including the review of Spurling and colleagues (2010), which suggests that exposure to industry information is

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positively related to lower prescribing quality and higher costs [31]. Nevertheless, this evidence is brought up to date and extended in the present review in several ways.

First, the updated meta-analysis (compiling recent data from France, the United States, and Denmark) reflects the association with the pooled odds ratio of 2.52, remarkably similar to that found by Spurling a decade ago. This evidence is robust over time and context, reinforcing confidence in the results.

Second, the French study by Goupil and colleagues (2019) shows a dose-dependent effect very well, as it included objective population-based data from the French Transparency in Healthcare database, which is associated with national prescribing records [10]. This approach helps avoid potential recall and social desirability bias that are present in many cross-sectional experiments.

Third, the qualitative research by Khan et al. (2023) in Pakistan sheds new light on the influence mechanisms in an LMIC setting [9]. Multiple psychological and social mechanisms have been demonstrated to govern the association between exposure to industry and prescribing behavior, so understanding these mechanisms is particularly important since they indicate that the influence is not a symptom of conscious corruption.

The principle of reciprocity, studied extensively by social psychologists, argues that the act of accepting a gift inculcates an unconscious sense of obligation to the giver [32]. Even minor, inexpensive gifts (a pen, a meal) activate this mechanism. Physicians who were given gifts from pharmaceutical representatives were unconsciously more likely to comply with their requests or to favor their products.

Cognitive dissonance theory, originated by Festinger (1957), suggests that people experience psychological distress if two contradictory beliefs or behavior oppose their values [33]. A physician who receives a gift from a pharmaceutical company but thinks accepting it would be an unwanted act may reduce their feelings of discomfort simply because they adjust their beliefs regarding accepting the gift — whether it means “the gift doesn’t affect me” or “everyone does it.” This change allows physicians easier access to gifts but also makes them more open to the company’s messages.

Although most physicians would agree that they are not personally influenced by industry interactions, they believe that colleagues are influenced [34]. This “it only affects my colleagues” bias decreases self-monitoring and vigilance to allow influence to act unknowingly.

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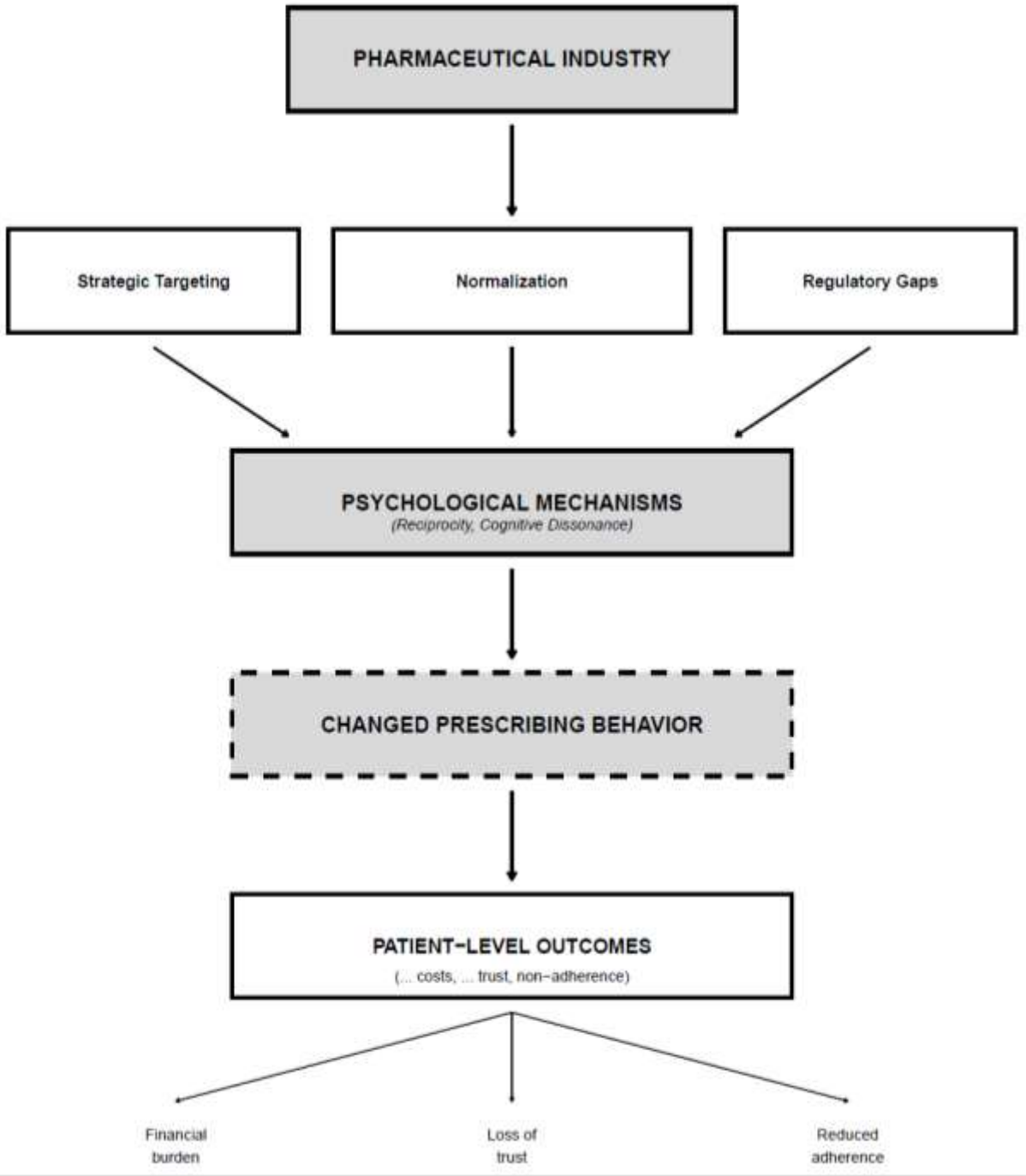
Figure 3: Synthesis of the pathways through which the pharmaceutical industry's influence operates.



Starting from the industry itself, three principal mechanisms have been identified through the qualitative literature: 1. Strategic targeting of high-volume prescribers; 2. Normalizing gift acceptance as a professional norm; and 3. Exploitation of regulatory gaps. These mechanisms activate well-known psychological processes. Particularly, reciprocity (through gifts creates an unconscious obligation) and cognitive dissonance (which leads physicians to change behaviors and beliefs to justify their acceptance) can be cited as examples. The results are altered

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prescribing behavior that can affect the patient through a more expensive financial burden, loss of trust in doctors, and adherence to treatment [17,18,29,30].

Our findings have important implications for multiple stakeholders.

Our results have important implications for different parties. First, strong regulatory frameworks are urgently needed. Regulatory ambiguity and weak enforcement have created fertile ground for abuse. Policymakers should delineate what kinds of interactions people are allowed or not allowed to do and invest in enforcement power. Second, public disclosure (similar to the US Physician Payments Sunshine Act) programs must be instituted in LMICs. Public disclosure provides patients with information about their physicians' personal ties to industry and accountability. Third, conflict-of-interest training must become a part of the medical curriculum and continuing medical education requirements.

First, professional associations should formulate and implement codes of conduct prohibiting or limiting industry links. Second, individuals in the healthcare field need to use alternatives to industry-funded information, such as academic detailing, characterized by independent professionals who offer evidence-based prescribing recommendations free of commercial impact. Third, health professionals should be required to disclose any industry relationship to their patients in the informed consent process.

Patients should be educated about the presence and potential implications of industry-physician relationships. Civil society organizations must promote transparency policies and educate patients on their rights. Patients can also ask their doctors directly about industry relationships and should feel empowered to seek second opinions when they have concerns.

This systematic review has several limitations that should be acknowledged.

Negative studies (those finding no association or a protective effect) are less likely to be published, and when they are published, they are less likely to be indexed or cited. This could lead to an overestimation of the true effect size.

The I^2 statistic for the meta-analysis was 64%, indicating substantial heterogeneity across studies. This heterogeneity is not surprising given the diversity of study designs, populations, settings, and exposure definitions. We attempted to explore this heterogeneity through subgroup analyses, but these analyses were limited by the small number of studies in each subgroup. Future research should aim to standardize exposure and outcome measures to facilitate meta-analysis.

We acknowledge that our subgroup analyses were conducted despite not meeting the pre-specified threshold of 10 studies per subgroup. This decision was made because we considered these exploratory analyses valuable for generating hypotheses about differential effects by exposure type, despite the limited statistical power. The wide confidence intervals observed (particularly for the CME funding subgroup, OR 2.77, 95% CI: 0.73–10.46) reflect this limitation, and these findings should be interpreted as hypothesis-generating rather than confirmatory. Future studies with larger numbers of studies are needed to provide more precise estimates for each exposure type.

Only 17.2% of included studies were from LMICs, and only one study (3.4%) was from Africa (South Africa). This severely limits the generalizability of our findings to the Malian and

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broader sub-Saharan African context, where regulatory environments, health financing structures, and pharmaceutical markets differ substantially from those in HICs.

Many cross-sectional studies relied on self-reported measures of industry exposure, which are subject to recall bias (physicians may not accurately remember past interactions) and social desirability bias (physicians may underreport interactions because they know it is socially disapproved). The few studies that used objective data (e.g., the French Transparency in Healthcare database) showed similar effects, suggesting that self-reported measures may be valid, but the possibility of bias remains.

The available studies focused exclusively on intermediate outcomes: prescribing patterns and costs. No study measured final clinical outcomes such as patient mortality, morbidity, or quality of life. It is possible (though unlikely) that the higher-cost, branded drugs promoted by industry produce better clinical outcomes, which might justify their higher cost. The available literature does not allow us to assess this possibility.

CONCLUSION

This systematic review confirms that interactions between healthcare professionals and the pharmaceutical industry are strongly associated with lower-quality, more costly, and less rational prescribing. The pooled odds ratio of 2.52 indicates that exposed physicians are more than twice as likely to prescribe irrationally compared to unexposed physicians. The effect is dose-dependent and persists even for small gifts. The mechanisms of influence include normalization, strategic targeting, and regulatory contradictions, operating through well-established psychological mechanisms such as reciprocity, cognitive dissonance, and optimism bias.

Despite the strength and consistency of this evidence, our review has identified three major gaps that should guide future research.

The evidence base for our primary population of physicians is heavily skewed toward HICs, particularly the United States. No study has documented the nature, extent, or consequences of industry-physician interactions in Mali or elsewhere in sub-Saharan Africa, despite rapid private pharmaceutical market growth and weak regulatory oversight. This gap is not merely academic; it has direct implications for patient care and health system performance.

No empirical study has analyzed whether industry influences the development of national or local clinical protocols. This is a potentially high-leverage pathway of influence that has been entirely neglected by researchers.

Although the limited available evidence suggests that patients are aware of industry-physician relationships, that their trust is eroded by this awareness, and that they demand transparency, patient voices are rarely integrated into research. Future research should systematically capture patient experiences and preferences.

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