Influences of the Pharmaceutical and Device Industries on Health Students: Could they be Controlled by Institutional Policy? A Systematic Review

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Abstract

Purpose: *The objective of this systematic review was to investigate whether health students' beliefs, attitudes, or behaviours are impacted by institutional policy about pharmaceutical and medical device industries PMDIs.*

Methods: Systematic review methodology. The authors searched BioMed Central, Catalogue of medical theses in France, CINAHL, Clinical Trials, Cochrane Libary, EMBASE, ERIC, Google Scholar, HAL, LILACS, PsycInfo, PubMed, Sage Journals, Web of Science, and WHO-ICTRP up to July 2018. They included randomised and non-randomised controlled trials, controlled before-after studies, cohort studies, cross-sectional studies with association measure and correlation models. Two investigators assessed the risk of bias of included papers by Cochrane Collaboration's tools.

Results: *Fourteen papers were included. Twelve were conducted on medical students, and one on dental students. Most studies are at an uncertain risk of bias. Institutional policies never have a significant effect on student contact frequencies with PMDIs. Student prescribing practices appear to be impacted by institutional policies. Exposure to institutional policy (versus no exposure, a shorter, or a less restrictive exposure) was found to predict higher quality prescriptions by students and was also a predictor of less frequent student prescribing.*

Conclusion: *There is still little evidence of how the most effective institutional policies work and their long-term effects are still limited, although more and more countries are implementing such policies. The implementation of such policies should be accompanied by a systematic and rigorous evaluation of their effectiveness.*

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Keywords: Health students; Pharmaceutical Industry; Health Policy; Interprofessional relationship; Behaviours

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Introduction

Rationale

In last decades, health "scandals" have been reported in the mass media such as thalidomide, blood transfusions contaminated by the HIV, Vioxx, Mediator (in France), etc. We can suppose that these cases, involving industrial actors responsibility, have had an impact not only on mortality or quality of life [1,2,3] but also on public trust in healthcare systems [4,5,50].

The data, probably underestimated, about the investment in pharmaceuticals sales force and marketing channels by the worldwide industry reached nearly $71 billion US dollars in 2014 [51]. The reports of the PMDIs with the highest sales performance show that sales promotion expenses, mainly targeted at healthcare personnel, constitute one-third of total turnover, about twice as much as research and development expenditure [49]. Yet, in 2010, Spurling et al. conclude that physicians most exposed to PMDIs prescribe more frequently, with higher costs, and yet have a lower prescribing quality [7]. More recently, systematic reviews and meta-analysis have confirmed these results [8,9].

These promotional actions are also targeted at healthcare students. Medical, dental, pharmacy, and nursing students are often exposed to industries during their training all over the world [9,10,11,12,13]. These exposures take various forms: interactions with drug representatives, receiving product information, drug samples, textbooks, gifts, or meals from PMDIs, participation in courses, workshops, or educational rounds organized or funded by PMDIs, etc. [9,10,11,13]. It has been shown that trainees are more vulnerable to PMDIs than senior physicians [14,15] and their exposure to PMDIs during training influence their future attitudes and behaviours [9,10,15,16].

A form of regulation of the interactions between PMDIs and healthcare students could be the introduction of lessons about conflict of interest management in the medical curriculum [17]. Several literature reviews conclude that trainees' attitudes and behaviours may be affected by curricula about trainees–pharmaceutical industry interactions [18,19,20]. However, the risk of bias for these studies is high or uncertain.

Another form of regulation is the introduction of policies to limit these interactions. In 2007, the American Medical Student Association (AMSA) released the first scorecard that graded medical schools on the presence or absence of a policy regulating the interactions between their students and faculty, and PMDIs [17]. Sixty-eight percent of American medical schools in the United States received an A (excellent or model policies) or B (good or solid policies) on AMSA scorecards in 2016 [52]. In other countries such as France, these policies are even less present [17] and the impact of these policies is not well known.

No review has looked at the effects of institutional policies on attitudes and behaviours since Carroll et al. in 2007 [19], while in the last fifteen years, several countries such as the United States of America [27], Australia [28], Canada [29], and France [53] have implemented institutional policies in medical schools to protect the independence of training from industry. More of that, no review has focused on other student populations than medical students.

Objective

Our objective was to determine whether, and to what extent, healthcare students' beliefs, attitudes, or behaviours are impacted, during or after their training, by institutional or legislative policies impacting the organisation of curricula or internship related to the interactions with the PMDIs.

Methods

We conducted a systematic review. We followed a detailed methodology (based on the recommen-

dations of the Collaboration Cochrane [54]) that we registered in PROSPERO International prospective register of systematic reviews. The report of the review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search strategy

We systematically queried the following databases for studies published before July 12, 2018: BioMed Central, Catalogue of medical theses in France, CINAHL, Clinical Trials, Cochrane Libary, EMBASE, ERIC, Google Scholar, HAL, LILACS, PsycInfo, PubMed, Sage Journals, Web of Science, and WHO-ICTRP. The search combined terms for health students, the pharmaceutical industry, and outcomes. For more details on the search strategies used within each database. In addition, we reviewed the references lists of included and relevant primary studies and literature reviews.

Eligibility criteria

The inclusion criteria were:

Type of study design: randomised controlled trials (RCTs), cluster RCTs, quasi-RCTs, controlled before-after studies, cohort studies, case-control studies, cross-sectional studies in which one or more association measures of the relationship between two or more variables were performed. We also will include cross-sectional studies using a double-difference approach or correlation models.

Type of participants: health students whose future profession is recognized with a state certificate in France and any health professional if the exposure being studied takes place during their training period.

Type of exposure: institutional or legislative policies impacting the organization of curricula or internship relating to the interactions with the PMDIs (with or without associated measures).

Type of control: either no exposition or a lower level of exposition.

Type of outcomes: knowledge, beliefs, attitudes, and behaviours (primary outcome) of healthcare students. Any reported health consequences for the patients. Estimates of absolute costs or any assessment of the cost-effectiveness of students' and professionals' practice for the states or the patients.

Languages: English, Esperanto, French, German, Italian, Portuguese, Spanish.

Studies selection

We first made a selection by title. Duplications due to overlap in the coverage of the databases and off-topic studies were excluded. Secondly, the abstracts of each study were analysed. Studies that did not meet the eligibility criteria on the basis of the content of their abstracts were excluded. Full-texts of the remaining studies were purchased and the eligibility criteria were again applied.

For references obtained with the complementary approach, the study abstracts were analysed and, if required, the full-text versions obtained to determine whether the studies met our eligibility criteria.

Data extraction

The data extracted included: study design, date of publication, country, participant characteristics, independent variables, data collection method, validity of measures and tools used, main outcomes and results, authors' conclusion and source(s) of research funding, and potential conflicts of interest. We contacted the authors of when data were missing.

Assessment of risk of bias

For RCTs, we used the Cochrane Collaboration's tool (RoB 2.0) for assessing the risk of bias [54]. For analysis of non-RCTs, we used a Cochrane Bias Method Group's tool: the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) [30]. One author assessed the risk of bias independently for each study and any hesitation was resolved by consulting a second author. For the "confounding domain" item, we searched the literature for a known confounding domain for each association of dependent and independent variables.

Data synthesis

We did not do any meta-analysis because the included studies are not sufficiently homogeneous for our primary outcome (ie. students' behaviours). We consider several types of synthesis of evidence including narrative synthesis and table.

We used considerations recommended by GRADE to assess the quality of the body of evi-

dence for each outcome and to draw conclusions about the quality of evidence within the text of the review [31].

Results

Of the 4 181 article titles identified by our standard search procedure, 14 articles met our inclusion criteria. Our complementary search strategy gave 11 more articles with 1 meeting our inclusion criteria. Reasons for exclusion after reading the abstract or the full-text was the type of study design (n=186), the participants (n=41), the accessibility (n=8) or several of these reasons and/or exposure (n=66). See Figure 1 for the flow chart of the study selection process.

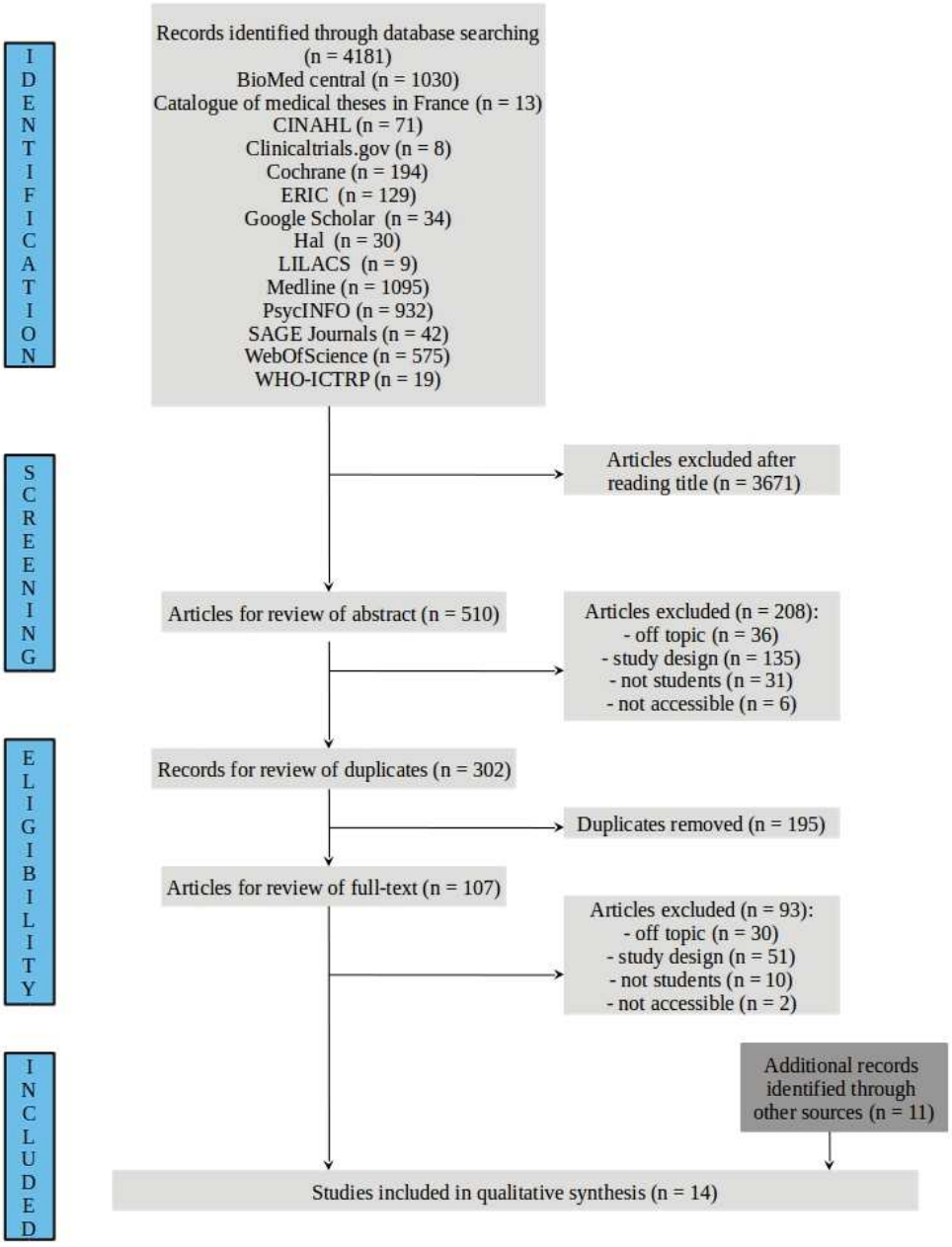

Figure 1. Flowchart of the study selection process.

Characteristics of included studies

Table 1 shows the characteristics of the 14 included studies. The design for the majority of studies was cross-sectional (n=7) [13,22,24,25,34,37,38]. Most studies were conducted in the USA (n=13) [21,22,23, 24,25,26,32,32,33,34,35,36,38], while one other was conducted in Canada (n=1) [37]. Only medical(n=13)[21,22,23,24,25,26,32,33,34, 35,36,37,38] and dental (n=1) [13] students were studied. The types of dependent variable assessed were students' beliefs, knowledge, or attitudes (n=5) [22,23,25,34,38], students' prescribing behaviours (n=8) [13,21,24, 26,32,33,35,36] and student's interaction behaviours (n=4) [24,25,36,37]. Table 2 shows a full detailed list of the independent variables investigated. Studies compare the absence with the presence of institutional policies (n=9) [13,26,32,33,34,35,36,37,38], more or less restrictive institutional policies (n=7) [21,22,23, 24,25,26,33], or a variable duration of exposure of students to the established institutional policy (n=1) [26]. These policies are implemented in medical or dental schools (n=6) [13,22, 23,24, 25,26] internship programs (n=4) [21,33,37,38], or health care centers (n=4) [32,34,35,36]. The types of policies assessed were too numerous to be cited in a comprehensive way, but they are briefly summarized in the Table 1. Some concern only the distribution of generic drugs (n=1) [36], or the prohibition of receiving drug samples (n=4) [13,32,33,35], while others regulate multiple aspects of interactions between students and industries (n=9) [21,22,23,24 ,25,26, 34,37,38].

Table 1. Characteristics of included studies

Authors, year, risk of bias	Study design	Participants	Exposure	Outcomes	Results
Lurie et al. 1990 ?	CSS	United-states Internal medicine residents from two of the teaching programs from seven Midwest teaching hospitals N=131 Participation = 75%	Contact with PMDI	Changing the prescription'practices	1/14 significant Only brief conversations independently predicted residents changes in practice (r=0.049)
Brotzman et Mark 1993 ?	CSS	United-states Family medicine residents from 14 randomly selected programs N=265. Participation = 70%	Institutional policy (contacts withs PMDI)	Contacts with PMDI Attitudes and beliefs	2/2 significant Exposure to pharmaceutical representatives was positively correlated with perceived benefit (r=0.638) and negatively correlated (r=0.706) with ratings of appropriateness of gift acceptance
Keim et al. 1993 ?	CT	United-states Emergency medicine residents N=1385. Participation=75%	Educational intervention (bioethic) Contact with PMDI and attitudes	Kowledge of bioethics Attitudes	2/? significant The resident knowledge was positively correlated (r=0.19) with the number of hours of bioethics training they reported receiving Residents' sensitivity to bioethical issues is negatively related to their number of contacts with PMDI (r=0.16)
Vinson, Candless & Hosokawa, 1993 -	CT	United-states First and second-year medical students N=139. Participation=67,5%	Educational intervention (50min) VS no educational intervention	Attitudes (acceptance of gifts)	1/1 significant The difference between the groups after the intervention was statistically significant (p<0.0001)
Hodges 1995 ?	CSS	Canada Psychiatry residents, interns and clerks from seven teaching hospital affiliated with the University of Toronto N=74. Participation=70%	Contact with PMDI	Attitudes and beliefs	2/45 significant The amount of money residents received was positively correlated (r=0.31) with their stating that they would have the same degree of contact with representatives if no promotional gifts were offered The number of promotional items received was positively correlated (r=0.24) with the belief that discussions with representatives have no impact on prescribing behaviour

Table 1. Characteristics of included studies *(cont.)*

Spingarn, Berlin & Strom 1996 ?	CSS	United-states Internal medicine residents from one university hospital N=75	Contact with PMDI (grand round)	Prescription intention (appropriate or not)	2/8 significant The residents who had attended the grand rounds were more likely to choose appropriately the cephalosporin manufactured by the speaker's company over other drugs for patients with Lyme disease presenting with second-degree heart block (OR=8.4; 95% CI 2.1-38.9) They chose it inappropriately for first-degree heart block (OR= 7.8; 95% CI 1.6-45.5)
Hopper, Speece & Musial 1997 ?	CBA	United-states Internal medicine residents from one university N=21. Participation=82,5%	Educational intervention	Attitudes and beliefs	3/8 significant After the intervention, residents who had attended the intervention showed an increased belief that PMDI representatives may use unethical marketing practices ($p<0.01$), that marketing gifts with no patient benefit may be inappropriate ($p=0.05$), and that other physicians' prescribing patterns could be negatively influenced through the acceptance of gifts ($p<0.05$)
Brewer 1998 ?	C	United-states Family medicine residents from two residency programs N=72	Institutional policy	Prescription behaviours (main outcome: NSAIDs)	5/27 significant There was a greater percentage of generic prescriptions (LR=0.87; 95% CI 0.79-0.95) and use of preferred NSAIDs (LR=0.83; 95% CI 0.75-0.92) but no decrease in the "cost per prescription" in the programs that limited or eliminated samples when compared to the program with an "open" sample policy.
Ferguson 1999 ?	CSS	United-states Internal medicine residents from a medical school hospital and two affiliated community hospitals N=346. Participation=40%	Institutional policy	Contact with PMDI representatives (number of meetings and sample acceptance)	No statistically significant results
McCormick 2001 ?	CSS	Canada Physicians who was internal medicine residents from two university in 1992 N=205. Participation = 69%	Institutional policy Contact with PMDI during residency	Contact with PMDI after graduation Attitudes	5/12 significant Policy during training remained a significant independent predictor of perceived benefit of PMDI information, with an OR of 0.37 (95% CI 0.14-0.96) for the program with policy about PMDI vs the program without Greater frequency of contact with PMDI during training was a predictor of increased perceived benefit of PMDI information (OR= 1.29; 95% CI 1.13-1.47) and was positively correlated with the current contact score ($r = 0.49$; $P<.001$)
Schwartz, Kuhles & Wade 2001 ?	C	United-states Psychiatry residents from psychiatric residency training clinic N=?	Contact with PMDI	Prescription behaviours (13 drugs)	12/13 significant Eleven out of 12 companies' visits were statistically associated with an increase in new medication starts ($p< 0.05$). As the number of sales visits increased, a greater statistical significance was noted.
Boltri, Gordon & Vogel 2002 ?	C	United-states Family medicine residents from the outpatient clinic (and family physicians) N=24	Institutional policy (drug samples)	Prescription behaviours	1/1 significant Prescription of first-line medication increased after sample distribution was prohibited (OR=2.73, 95% CI=1.29-5.76)
Adair & Holmgren 2005 +	RCT	United-states Internal medicine residents in an primary care clinic N=29	Institutional policy (drug samples)	Prescription behaviours	5/13 significant Resident physicians with access to drug samples were less likely to choose unadvertised drugs than residents who did not have access to samples ($p= 0.04$) and less likely to choose over-the-counter drugs ($p= 0.003$)
Huang et al. 2005 ?	C	United-states. Psychiatry residents from an adult outpatient clinic N=?	Contact with PMDI (conferences)	Prescription behaviours (25 drugs)	6/6 significant Strong positive correlation ($r=0.87$) between pharmaceutical company sponsorship of resident conferences and the use of the corresponding antidepressant by patients.

Table 1. Characteristics of included studies *(cont.)*

Huang et al. 2005 ?	C	United-states. Psychiatry residents from an adult outpatient clinic N=?	Contact with PMDI (conferences)	Prescription behaviours (25 drugs)	6/6 significant Strong positive correlation (r=0.87) between pharmaceutical company sponsorship of resident conferences and the use of the corresponding antidepressant by patients.
Randall et al. 2005 ?	CT	United-states Psychiatry residents from two clinics N=43. Participation = from 64 to 82%	Educational intervention (1h30)	Contact with PMDI (gift acceptance) Beliefs and attitudes	2/4 significant Compared to the comparison group, the intervention group significantly decreased the reported number of office supplies (p=0.0001) and non-educational gifts (p=0.032), but showed no change in attitude toward pharmaceutical representatives and their gifts
Schneider 2006 -	C	United-states Internal medicine residents from one university N=161. Participation = from 80 to 91%	Educational intervention (one session)	Attitudes	1/6 significant The intervention group was more likely to rate only one item, "lunch at noon conference," as less appropriate (p = 0.042).
Hyman 2007 +	CSS	United-states Medical students (year one to five) from one university N=406. Participation = 58%	Attitude (feeling educated to about about PMDI professionals' interactions)	Attitudes	5/5 significant Students who reported feeling better educated about pharmaceutical industry interactions tended to be less sceptical of the industry and more likely to view interactions with the industry as appropriate (gift acceptance r=0.12; gift presentation r=0.21; sponsored events acceptance r=0.17).
Alvero &Panganiban 2008 ?	RCT	Philippines Third-year medical students from one university N=185	Educational intervention (2x2h) VS two sessions of video presentations on herbal medicine preparation	Knowledges (identification of violations of existing guidelines governing medicinal drug promotion)	1/1 significant There was no significant difference in the baseline scores of the two groups but the post-intervention scores were significantly higher in those who underwent the teaching module on critical appraisal of medicinal drug promotion (p < 0.000)
Alvero &Panganiban 2008 ?	RCT	Philippines Third-year medical students from one university N=185	Educational intervention (2x2h) VS two sessions of video presentations on herbal medicine preparation	Knowledges (identification of violations of existing guidelines governing medicinal drug promotion)	1/1 significant There was no significant difference in the baseline scores of the two groups but the post-intervention scores were significantly higher in those who underwent the teaching module on critical appraisal of medicinal drug promotion (p < 0.000)
Civaner et al. 2008 ?	CSS	Turkey Nursing students (year one to four) from two universities N=442. Participation = 75,2%	Contact with PMDI (indirectly through observation or directly by first-hand experience)	Attitudes and beliefs	15/15 significant The exposure of students to the marketing methods of pharmaceutical companies increases the probability that students will adopt rationales that underlie affirmative judgments of health worker–PMDI relationships (OR from 1.598 95% IC 1.006-2.538 to 3.576 95% IC 1.613 to 7.925)
Markham, Diamond & Fayock 2008 ?	CBA	United-states Family medicine residents from one university and three affiliated sites N=243	Educational intervention (4 sessions)	Attitudes	1/1 significant The exposed students have an attitude score less favourable to PMDI (p=0.0372) than presentations after the intervention
Dekker & Craen 2009 ?	RCT	Netherlands Second-year medical students from one university N=172	Gift (pen) and compliments	Beliefs	1/1 significant Of the students who did not receive a pen, only four believed the authenticity of at least one of the slides (RR=3.9, 95% CI 1.4–10.8)
Grande et al. 2009 ?	CT	United-states Third and four-year medical students N=187. Participation=53,1%	Small pharmaceutical promotional items	Implicit et explicit attitudes on treatment preferences	2/4 significant Fourth-year students exposed to Lipitor promotional items had more favourable implicit attitudes about that brand-name drug compared to the control group (p= 0.05)

Table 1. Characteristics of included studies *(cont.)*

Grande et al. 2009 ?	CT	United-states Third and four-year medical students N=187. Participation=53,1%	Small pharmaceutical promotional items	Implicit et explicit attitudes on treatment preferences	2/4 significant Fourth-year students exposed to Lipitor promotional items had more favourable implicit attitudes about that brand-name drug compared to the control group (p= 0.05)
Benjamin, Swartz & Forman 2011 ?	C	United-states Psychiatry residents from one medical center in university N=100	Educational intervention (seven sessions) and generic drugs samples VS no intervention and no samples	Prescription behaviours (generic drugs)	3/3 significant The exposition increase overall generic prescribing (OR=1.12 CI 95% 1.05-1.20) and particularly large increase prescribing of generic antipsychotic medications (OR=1.39 CI 95% 1.25-1.55)
Hujoel et Gilette 2011 ?	CSS	United-states Predoctoral dental students, graduate students and faculty members from one spring quarter. N=175. Participation = from 71 to 86%	Branded drug samples from only one industry VS no control of drug-sample program	Prescription intention and justifications	4/4 significant Exposure to the branded drug sample was associated with an increase in the recommendation for the brand name (OR=11.9 95% CI 5.8-24.5) and for the therapeutic class to which the branded drug sample belonged (OR=2.6 95% CI 1.1-6.0) and with a reduction for considering other therapeutic classes (OR=0.34 95% CI 0.18-0.63) and aetiology (OR=0.16 95% CI 0.08-0.35)
Kao et al. 2011 +	C	United-states Second and third-year medical students from four medical schools N=482. Participation = 51,6%	Institutional policy Educational intervention (3 sessions) VS no intervention Contact with PMDI	Attitudes and beliefs	10/24 significant Intervention students were more likely to think that physicians are strongly or moderately influenced by pharmaceutical marketing (OR= 2.29; 95% CI, 1.46-3.59) and believed they would be more likely to prescribe a company's drug if they accepted that company's gifts and food (OR= 1.68; 95% CI, 1.12-2.52). Intervention students were more likely to support banning interactions between pharmaceutical representatives and students (OR= 4.82; 95% CI, 3.02-7.68) and with physicians (OR= 6.88; 95% CI, 4.04-11.70). Students from schools with more restrictive policies were more likely to support banning interactions between pharmaceutical representatives and students (OR= 1.99; 95% CI, 1.26-3.16) and with physicians (OR= 3.44; 95% CI, 2.05-5.79).
Austad et al. 2013 ?	CSS	United-states First and fourth-year medical students from all allopathic schools N=3495. Participation= from 43,1 to 49,3%	Institutional policy Public funding	Contact with PMDI representatives Attitudes and beliefs	2/6 significants Students in schools receiving more NIH funding reported industry gifts less often (OR = 0.51 95 % CI 0.38-0.68), but the strength of institutional conflict of interest policies was not associated with this variable
Epstein et al. 2012 ?	C	United-states Psychiatrists graduated in 2001 and 2008 N=1652. Participation=60,3%	Institutional policy during residency (about COI)	Prescription behaviours (heavily promoted medications and brand names)	6/6 significants Differences between pre-COI and post-COI graduates' prescribing of heavily promoted medications were larger for maximally restrictive programs than both minimally restrictive programs [-4.3 percentage points; 95% confidence interval (CI), -7.0, -1.6] and moderately restrictive programs (-3.6 percentage points; 95% CI, -6.2, -1.1). The difference in prescribing reformulations was larger for maximally restrictive programs than minimally restrictive programs (-3.0 percentage points; 95% CI, -5.3, -0.7)
King et al. 2013 ?	C	United-states Physicians graduated from 34 schools N=2449.	Institutional policy	Prescription behaviours	6/18 significant Physicians who attended a medical school with an active COI policy were less likely to prescribe lisdexamfetamine over older stimulants (OR=0.44, 95% CI 0.22-0.88;) and paliperidone over older antipsychotics (OR=0.25, 95% CI 0.07-0.85)
Austad et al. 2014 ?	CSS	United-states Fourth-year medical students and residents from all allopathic studies N=2336. Participation= from 42,9 to 49%	Contact with PMDI	Prescription intentions	4/16 significant A 10-point higher industry relations index was associated with 15% lower odds of selecting an evidence-based prescribing choice (OR=0.85; 95% CI, 0.79-0.92). Significant association between the industry relations index and greater odds of choosing to prescribe brand-name drugs (OR=1.08; 95% CI, 1.00-1.16).

Table 1. Characteristics of included studies *(cont.)*

Austad et al. 2014 ?	CSS	United-states Fourth-year medical students and residents from all allopathic studies N=2336. Participation= from 42,9 to 49%	Contact with PMDI	Prescription intentions	4/16 significant A 10-point higher industry relations index was associated with 15% lower odds of selecting an evidence-based prescribing choice (OR=0.85; 95% CI, 0.79-0.92). Significant association between the industry relations index and greater odds of choosing to prescribe brand-name drugs (OR=1.08; 95% CI, 1.00-1.16).
Etain et al. 2014 ?	CSS	France Medical residents from all schools N=2101. Participation=3,1%	Educational intervention Personal research about COI	Attitudes and beliefs	1/4 significant Personal research about COI is associated to belief that having received a gift will influence your future prescriptions (OR 2.69, 95% CI 1.25-5.44)
Jahnke et al. 2014 -	CSS	Germany Clinical medical students from one university N=702. Participation=55%	Contact with PMDI	Beliefs	0/1 significant
Montastruc et al. 2014 +	CSS	France Medical residents from six schools N=630. Participation=13,3 à 20%	Educational intervention about COI Beliefs	Contact with PMDI	1/2 significant Residents who had a more positive opinion were more frequently exposed to drug companies (OR=2.12 CI 95% 1.07-4.22)
Yeh et al. 2014 ?	CSS	United-states First and fourth-year medical students from all allopathic schools N=1610. Participation=49,3%	Institutional policy	Contact with PMDI Attitude	0/6 significant The association between policy and contact became non significant when fully adjusted for national institutes of health funding level.
Riese et al. 2015 ?	CSS	Europe Psychiatry residents N=1444. Participation=7,5%	Attitudes	Contact with PMDI	9/18 significant Assigning an educational role to the pharmaceutical industry was associated with more interactions and higher gift value (OR=1.18, 95% CI 1.02-1.37)
Riese et al. 2015 ?	CSS	Europe Psychiatry residents N=1444. Participation=7,5%	Attitudes	Contact with PMDI	9/18 significant Assigning an educational role to the pharmaceutical industry was associated with more interactions and higher gift value (OR=1.18, 95% CI 1.02-1.37)
Sierles et al. 2015 -	CSS	United-states Third-year medical students from eight universities N=866. Participation=68,2%	Contact with PMDI Attitudes	Contact with PMDI intention Attitudes	6/7 significant The scepticism and exposure indexes had a significant inverse correlation ($r = -0.149$), meaning that the more sceptical students were exposed less often
Yeh et al. 2015 ?	CSS	United-states Medical residents from all allopathic schools N=739. Participation=44%	Institutional policy Prescription intentions	Prescription intentions Contact with PMDI	0/12 significant (policy) Residents who correctly answered evidence-based prescription questions were about 30% less likely to have attended industry-sponsored lectures (OR = 0.72, 95% CI 0.56-0.98)
Beyhun et al. 2016 -	CSS	Turkey Final year medical students from one university N=154. Participation = 92,2%	Educational intervention (1 week) Contact with PMDI	Attitudes	10/152 significant Students with rational prescription training expressed greater agreement with the statement "I am sceptical concerning the information provided by drug companies during interactions" than those who had not received such training (OR=3.7 95% CI 1.2-11.5). Acceptance of advertisement brochures was found to significantly reduce the level of agreement with the proposition that "A physician should not accept any gift from a drug company." (OR=0.3 95% CI 0.1-0.9).
González et al. 2017 ?	CSS	Spain Medical residents in the Region of Madrid N=350. Participation =8,4%	Educational intervention (or not) Attitudes and skills	Attitudes and contact with PMDI representatives	8/12 significant Training in informal settings was associated with an interaction index ≤ percentile 25 (OR=2.83 95% CI 1.32-6.07)

Table 1. Characteristics of included studies (cont.)

González et al. 2017 	CSS	Spain Medical residents in the Region of Madrid N=350. Participation =8,4%	Educational intervention (or not) Attitudes and skills	Attitudes and contact with PMDI representatives	8/12 significant Training in informal settings was associated with an interaction index ≤ percentile 25 (OR=2.83 95% CI 1.32-6.07)

Note: CBA: before-and-after-study; C: cohorte study; CST: cross-sectional study; CT: controlled trial; RCT: randomised controlled trial;
NSAIDs: non steroidal anti inflammatory drugs; COI: conflict of interests; Green indicates a low general risk of bias, orange a moderate risk, yellow an unclear risk and red a high risk.

Risk of bias

The detailed judgments about each risk of bias item for included studies are displayed in Figure 2 for non-RCTs studies and Figure 3 for the RCT study.

For all non-RCTs studies, the risk of bias was judged to be low for "selection of participants", "deviations from intended interventions", and "selection of the reported results". The items judged with the most uncertainty or high or moderate risk of bias were those on "confounding", "measurement of outcomes", and "missing data".
Only two studies were at low [32] or moderate general risk of bias [23].

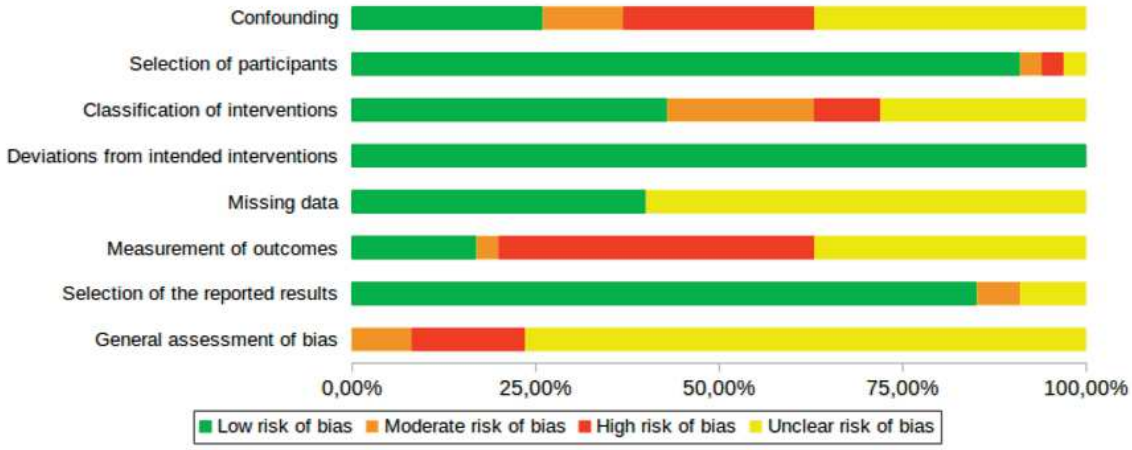

Figure 2. Detailed judgments about each risk of bias item for included non-RCTs studies.

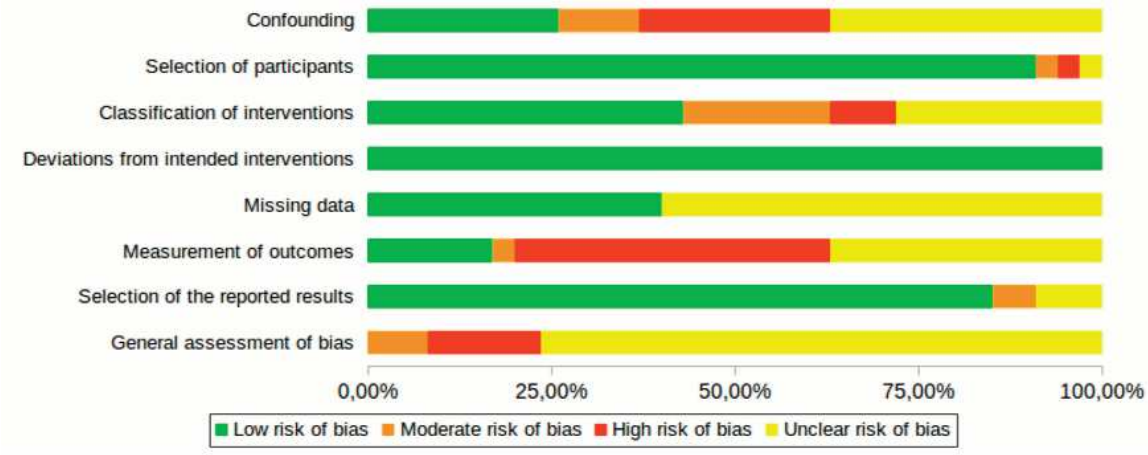

Figure 3. Detailed judgments about each risk of bias item for the included RCT study.

Summary of findings

Table 3 shows the quality of evidence by exposure and outcome. The quality of evidence for all comparisons according to GRADE approach is very low. The overall risk of bias assessment for each study is uncertain, moderate, or low, but never high. The results therefore highlight some trends. Table 2 shows the results sorted by outcome in more detail.

Firstly, institutional policies never have a significant effect on student contact frequencies with PMDIs [24,25,34,37]. Students exposed to institutional policies (versus those not exposed, exposed for less time, or exposed to less restrictive policies) are no less likely to accept meals [24] or gifts [24,25] from PMDIs representatives. They do not talk less often with them [24,25,37] and do not attend meetings or lecture less often [24,34].

Second, student prescribing practices appear to be impacted by institutional policies. Their quality was investigated in six studies [13,24,26,32,35,36]. Exposure to institutional policy (versus no exposure, a shorter, or a less restrictive exposure) was found to predict higher quality prescriptions in 62% (n=16/26) of the models performed. The frequency of prescriptions was investigated in two studies [21,33]. Exposure to institutional policy (versus no exposure, a shorter, or a less restrictive exposure) was also a predictor of less frequent student prescribing in 42% (n=11/26) of the models performed.

Third, institutional policies sometimes have effects and sometimes no effects on students' attitudes and opinions about PMDIs. The two opinions most frequently investigated were: 1) students' perceived benefit of the information provided by PMDIs [37,38]; 2) their perception of the adequacy of the separation between their faculty and PMDIs [22,25]. Exposure to institutional policy (versus no exposure, a shorter, or a less restrictive exposure) is a predictive factor of less favourable perceptions in respectively 67% (n=2/3) et 75% (3/4) of the models performed. However, when looked at more precisely the type of exposure, the results are consistent when looking at the opinions of students exposed to the policies versus those not exposed. Being exposed to policies (versus being not exposed) is a predictive factor of a less beneficial perception of information from PMDIs and appropriateness of gift acceptance from PMDIs in 100% (n=4/4) of the models performed [37,38].

The study of Adair and Holmgren [32] is the only included study with a low risk of bias and assess the effect of policy about drug samples. Unfortunately, its results are not widely generalizable because it concerns only 29 residents in one health center in the United States.

Discussion

Synthesis of the main findings

Fourteen articles were included about the relationship between healthcare students' beliefs, attitudes, or behaviours and institutional or legislative policies impacting the organization of curricula or internship relating to the interactions with the PMDIs. These studies are heterogeneous concerning exposures and outcomes. Most studies are at an uncertain risk of bias. The most studied participants are medical students.

The three main results are:

1) institutional policies never have a significant effect on student contact frequencies with PMDIs;

2) student prescribing practices appear to be impacted by institutional policies. Exposure to institutional policy (versus no exposure, a shorter, or a less restrictive exposure) was found to predict higher quality prescriptions by students and was also a predictor of less frequent student prescribing;

3) institutional policies sometimes have effects and sometimes no effects on students' attitudes and opinions about PMDIs.

Interpretation of findings

Only medical students are studied. Studies include only medical and dental students. There are no pharmacy or nursing students included although they are prescribers in some countries, and no rehabilitation personnel, even though they frequently use many medical devices. One interpretation of this absence is that they are less exposed and influenced by PMDIs, a hypothesis that is not confirmed by empirical studies on non-physician clinicians [39]. This absence could come from the keywords entered in the databases. However, the keywords did not focus on medical students in any of the databases (see Appendix 3). It is possible that the physicians' population is more studied because the social pressure regarding the importance of the physician's moral integrity is stronger. Perceptions of their legal and ethical responsibility may be greater than those of other healthcare professions [40].

Effect on prescribing behaviour but not on the frequency of interaction with industries. Institutional policies have no impact on the frequency of interactions between students and PMDIs, whether these interactions take the form of receiving gifts, sharing meals, speaking with representatives, or attending courses or conferences. Yet, these policies aim to restrict or even outlaw this type of interaction [24,25]. These behaviours (interacting or not with industries) are assessed in all studies through student questionnaires. Assessment is therefore subjective, and memory and social desirability biases [41] can bias student responses. In addition, the risk of bias in the item "measurement of outcomes" was rated as uncertain or moderate in 76% of the studies included. Now that databases exist in various countries in which contacts between health professionals and students and industries are reported in a systematic and required manner, these data could be preferred to self-administered questionnaires. This would validate or refute the hypothesis that institutional policies appear ineffective for these outcomes because of the methodological limitations of the evaluation of these outcomes.

Prescribing behaviours are assessed more objectively: students are not asked what they prescribe. Electronic data from consultations with patients in healthcare institutions are used.

Finally, the feeling of invulnerability (a variant of the bias blind spot) highlighted in students should lead to favouring studies not based on self-reported data. Medical students see the impact of PMDIs contacts on the judgement or action of their colleagues more than on themselves [22,23,42, 43,44]. They think they are less influenced than their peers. This bias is more frequent among students than graduates [44], among first-years students than last-years [22], and among students exposed to PMDIs than those unexposed [42]. The existence of this illusion of invulnerability among students should lead to interpreting the results of self-reported surveys on the frequency of interaction and the influence of industries even more cautiously. The results of this type of survey probably tend to reduce the frequency of interaction with industries and the influence of these interactions, because of the social desirability bias [41] but also because of this illusion of unique invulnerability.

Inconsistent effect on attitudes and opinions

Institutional policies sometimes have effects and sometimes don't on students' attitudes and opinions about PMDIs. Confounding factors may explain these inconsistent results, especially since the studies included are often at a risk of bias on this item. The influence of PMDIs is very complicated because it takes many different forms, and, national laws do not allow the same level of interaction. Curriculum contents also vary from country to country. Within the same country and for the same outcomes, results can still be contradictory [24,25], which highlights that other confounding factors exist.

The confounding factors most often considered in the studies included about institutional policies are: the medical speciality [26], the type of patients being cared for [32,33,34,36], the gender of

students [26], and the proportion of national institutes of health funding level [24,25]. For example, the association between policy and contact with PMDIs representative became non-significant when fully adjusted for national institutes of health funding level in the study of Yeh et al [24]. Other confounding factors may occur such as the national health system organization or federal laws.

Comparison to findings of similar reviews

Our results are partially consistent with previous systematic reviews. Carroll et al. [19] were more confident about the effects of institutional policy although the size of the empirical research body appears as modest, but they did not assess the risk of bias of included studies. Zipkin et al. [15] conclude that institutional policies are likely to be effective. They also suggested that the presence of policies is associated with more sceptical attitudes toward industry and fewer future interactions with representatives. These partially different results may be explained by the broader inclusion criteria by Zipkin et al. and Carroll et al. regarding the design of the studies included in their review. They did not assess the risk of bias in the included studies, but it is likely to be more important given the design of these studies (before and after study without control group, cross-sectional survey without consideration of confounding factors).

For over 10 years of research, these results are certainly of low or uncertain quality but stay consistent. Despite of that, the institutional policies of healthcare students have not really changed . This raises the question of how long it takes for evidence to be incorporated into practice, not only for clinical practices but also and above all for education systems.

Implications for research

The high prevalence of interactions between health students, professionals, and PMDIs is well documented [9,10]. The impact of these interactions on the quality of care as well, although there is lower quality evidence [9,10,15,16]. On the other hand, there is still little evidence of how the most effective institutional policies work and their long-term effects are still limited and of low quality. For example, no empirical study assesses the state policies on transparency which have been in effect worldwide since 2007, although several authors question their relevance [45]. It is important to note that relevant strategies exist for making evidence-based medicine in the therapeutic plan, but we do not have the methodological means to make evidence-based health policy even though it is necessary.

Our findings show the recurrent risk of bias of studies about healthcare students, institutional policies, and PMDIs, which must be taken into account for future studies on this topic. The first is the use of non-validated questionnaires. Lotfi et al. [46] alert on the poor quality of tools used in surveys of physicians and PMDIs, which are also the support for studies about students. The second is the management of missing data. This information is often missing in research, especially regarding the treatment of questions that students did not answer in the questionnaires. The third risk of bias results from confounding factors. Most authors do not justify the choice of controlled or uncontrolled confounders, and when they do, they do not necessarily use the available literature.

Finally, the feeling of invulnerability highlighted in students should lead to favouring studies not based on self-reported data to assess the influence of PMDIs' interactions on students. For example, data collected by hospitals or governments on prescriptions or purchases made by students may be preferred to questionnaire surveys.

Implications for practice and policy

Given the empirical evidence of the relationship between students and PMDI, this topic should be addressed in the curricula of health students. This is not the case according to studies on the subject [43,47], as students are claiming [47]. The existence of bias blind spot among medical students should even more likely lead to the achievement of these

teachings. Guidelines translated into several languages and based on the literature are suggested to implement these teachings [55].

Schools training health professionals, if they wish to limit the negative impact on the quality and quantity of prescriptions generated by interactions between students and industries in the short term, should implement and especially assess the effectiveness of institutional policies to regulate these interactions. Concrete measures can be taken: distribution of generic drugs, prohibition of receiving drug samples, meals, or gifts from PMDI, and to prohibit courses, talks, or conferences by PMDI representatives.

The effect of restrictive policies toward PMDIs in medical schools and faculty may not last if the students are no longer in a restrictive environment after graduation or during their internship. Similar restrictive policies should therefore be adopted for both healthcare students and professionals.

Some go so far as to propose an entirely new system where drug research and development will be a public enterprise, with no patents, and defined entirely by the public interest [48].

Strengths and weaknesses of the review

The major strength of this systematic review is its exhaustiveness. Exhaustiveness was ensured by the use of several important bibliographic databases (n=15), the use of an elaborate research strategy, the systematic use of the 'benefit of the doubt' in the selection process of articles, and the implementation of in-depth additional research (the reading of the bibliographies of articles included concerned more than 500 references). In addition, we used Cochrane tools for conducting the review and GRADE approach for summarizing the quality of evidence. Methodological improvements for future studies have thus been reliably identified.

A potential limitation of our review is that we searched only in English or French in the electronic databases. However, the inclusion criteria allowed articles to be included in seven languages. The databases searched included articles with titles or abstracts translated into English or French. Access to non-English or French literature was therefore still possible. Other limitations relate to the uncertain quality of most of the studies found. However, uncertain or low-quality evidence from empirical studies is always better than personal points of view to understand a complex, high-stakes topic on which myths persist. On the other hand, our analysis of the risk of bias should be considered with caution. The ROBINS-I tool proposed by the Collaboration Cochrane provides a rich and valid analytical framework for the evaluation of non-RCTs, but its metrological qualities are still under evaluation [30]. For example, there is not yet an algorithm concerning the criteria to be considered for each item, as was done for the Cochrane tool for RCTs [6].

Despite the uncertain quality of most included studies, this review adds some important knowledge to the existing literature. Firstly, it highlights the most frequent risks of bias in studies conducted on the topic to improve future studies. Secondly, it shows that only interactions between PMDIs and medical students are really studied. Students in pharmacy, dentistry, nursing or rehabilitation are not or rarely studied on the topic. Thirdly, the review suggests that there is little assessment of the impact of institutional policies that have sometimes been in place in faculties for several decades.

Conclusion

Effects of institutional policies impacting the organization of curricula or internship relating to the interactions with the PMDI on healthcare students' beliefs, attitudes, or behaviours are studied mainly among medical students. Most studies are at an uncertain risk of bias. Institutional policies never have a significant effect on student contact frequencies with PMDIs but students' prescribing practices appear to be impacted by institutional policies. Exposure to institutional policy (versus no exposure, a

shorter, or a less restrictive exposure) was found to predict higher quality prescriptions by students and was also a predictor of less frequent student prescribing. Institutional policies sometimes have effects and sometimes no effects on students' attitudes and opinions about PMDIs. There is still little evidence of how the most effective institutional policies work and their long-term effects are still limited, although more and more countries are implementing such policies [17]. The implementation of such policies should be accompanied by a systematic and rigorous evaluation of its effectiveness.

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Conflict of interest

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Resumo

Taksi ĉu kaj kiel, la kredoj, sintenoj kaj agmanieroj de sanstudantoj estas influataj per interagado kun la san-firmaoj kaj industrioj, per specifaj pedagogiaj agadoj kaj per instituciaj politikoj.

Ni faris sisteman sciencliteraturan sintezon. Observadaj kaj eksperimentaj studoj taksante la interagadojn de sanstudantoj kaj sanfirmaoj estis elekteblaj. Ni serĉadis per 14 datumbazoj ĝis januare 2018. Ni analizis la biasojn de ĉiu studo per la iloj de la internacia Collaboration Cochrane. Ni taksis la ĝeneralan kvaliton de la studaro per la metodo GRADE.

Post aplikado de niaj elekt-kriterioj ni konservis 38 artikolojn. Plejofte temis pri studoj pri medicino-studantoj (n=36) kaj usonaj sanstudantoj (n=27). Pli ofte estas taksataj la sintenoj kaj agadmanieroj de la studantoj (n=22), poste iliaj interagadoj kun industrioj (n=12) kaj fine iliaj preskrib-agadoj (n=9) kaj preskrib-agadaj intencoj (n=3). La plimulto de la studoj havas malcertan biasoriskon (n=30) kaj nur unu havas malfortan biasoriskon. Kiam la rezultoj estas signifaj, ĉiam ili montras efikecon de la instituaj politikoj kaj pedagogiaj agadoj, pri malpliiĝo de la preskriboj kaj pliboniĝo de iliaj kvalito, pri malpliiĝo de la interagado kun industrioj kaj pri malpli favoraj kredoj kaj sinteno pri ili.

La pruvnivelo de la studaro estas tre malforta por ĉiuj dependaj variabloj taksitaj. Tamen la rezultoj konverĝas al efikeco de la instituaj politikoj kaj de la pedagogiaj agadoj centrataj pri la interagadoj kun san-firmaoj kaj industrioj por plibonigi la preskribajn agmanierojn de la sanstudantoj.

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