BMJ Open

Sunshine on KOL : a retrospective study about financial ties between medical key opinion leaders and pharmaceutical industry in France.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051042
Article Type:	Original research
Date Submitted by the Author:	09-Mar-2021
Complete List of Authors:	CLINCKEMAILLIE, Marie; Université Cote d'Azur, Département d'Enseignement et de Recherche en Médecine Générale, RETINES, HEALTHY SCANFF, Alexandre; [(Centre d'Investigation Clinique de Rennes)] Naudet, Florian; [(Centre d'Investigation Clinique de Rennes)] BARBAROUX, Adriaan; Université Cote d'Azur, Département d'Enseignement et de Recherche en Médecine Générale, RETINES, LAPCOS, HEALTHY
Keywords:	ETHICS (see Medical Ethics), HEALTH ECONOMICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Public health < INFECTIOUS DISEASES

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Sunshine on KOL : a retrospective study about financial ties between medical key opinion leaders and pharmaceutical industry in France.

Marie CLINCKEMAILLIE, MD (ORCID: 0000-0001-6643-001X)[1], Alexandre SCANFF, MD (ORCID: 0000-0001-5419-817X)[2], Florian NAUDET, PhD (ORCID: 0000-0003-3760-3801)[2], Adriaan BARBAROUX, MD (ORCID: 0000-0002-9243-6922)[3].

[1]Université Cote d'Azur, Département d'Enseignement et de Recherche en Médecine Générale, RETINES, HEALTHY, France
[2]Univ Rennes, CHU Rennes, Inserm, CIC 1414 [(Centre d'Investigation Clinique de Rennes)], F- 35000 Rennes, France
[3] Université Cote d'Azur, Département d'Enseignement et de Recherche en Médecine Générale, RETINES, LAPCOS, HEALTHY, France

Corresponding author : A. Barbaroux
Adriaan.barbaroux@univ-cotedazur.fr; 2bis Avenue Durante, 06000 Nice

Word count of the manuscript text : 2985

ABSTRACT

Objective

To investigate the nature, extent and evolution of financial relationships between key opinion leaders (KOL) or non-KOL physicians and pharmaceutical and device companies in France.

Design

Retrospective and descriptive study

Setting

All doctors practicing in France, with a focus on 548 KOL defined as board members of all the professional medical associations having published clinical practice guidelines in 2018 or 2019. These 99 associations were identified by the cross-checking of 3 databases.

Main outcome measures

The number and the amount of gifts (year by year since 2014), remunerations and agreements (year by year since 2017).

Results

Physicians had 818m€ ($936m, £741m) of gifts declared from 2014 to 2019. 83% of KOL had such links of interest. The 548 identified KOL represented 0.24% of physicians in France but received 1.5% of the total amount of gifts, i.e. €12.3m ($14m, £11m or €3 700 per capita per year).

Physicians had 125m€ ($143m and 114m£) of agreements declared from 2017 to 2019. The 548 KOL received 0.72% of the agreements and 2.5% of the value of the agreements, i.e. 3.1m€ ($3.6m, £2.8m) or €1 900 per capita per year ($2200, £1700).

Physicians had 156m€ ($178m and 141m£) of remunerations declared from 2017 to 2019. The 548 identified KOL received 4.4% of the total value of remunerations to physicians, i.e. 6.8m€ ($7.8m, £6.2m) or 4 100€ per capita per year ($4 800, £3 700).

Almost every professional medical associations (99%) had in their board at least one KOL with a financial tie.

Conclusion

Financial relationships between KOL and the industry in France are extensive, KOL have much more financial ties than non-KOL practitioners. The main limit of this study arises from the quality of information provided on the French Transparency in Healthcare database.

Pre-registration: osf.io/m8syh

Strengths and limitations of this study

This is the first attempt to provide data on the extent of the links of interest between opinion leaders and pharmaceutical industry in France.

Author crossed the nationwide databases of financial ties with three databases of professional medical associations.

All medical doctors practicing in France were inclused, with a focus on 548 KOL defined as board members of all the professional medical associations having published clinical practice guidelines in 2018 or 2019.

These 99 associations were identified by the cross-checking of 3 different catalogs of French professional associations.

The major links between key opinion leaders and industry ask the question of the independence of the experts, and raises concern that guidelines can be influenced by industry.

Keywords :
Conflict Of Interests – Key Opinion Leaders – public health – quality in health care – medical ethics

INTRODUCTION

Financial ties between healthcare workers and pharmaceutical indusctry may affect every aspects of medical activity, from research to clinical practice. Clinical trials and meta-analyses sponsored by the pharmaceutical industry are more likely to conclude that drugs are effective than non-sponsored trials. [1] Industry's transfers of value to physicians have been shown to be associated with more expensive, more frequent and of lower quality prescriptions[2–5] . Recommendations for clinical practice, which define the diagnostic criteria and treatment of the diseases, can also be under influence, since their authors often have ties with the industry. [6–11]

Following the example of the USA with the US Physician Payments Sunshine Act, France created the Transparency in Healthcare public database (transparence.santé.gouv.fr) in 2014. [12–14] Pharmaceutical and medical device industries are required by law to disclose gifts, agreements and remunerations they transfer to healthcare professionals in France.

The term "Key Opinion Leaders" (KOL) refers to physicians who influence their peers' medical practice, including but not limited to prescribing behaviour. It was coined by sociologists who demonstrated that people changed their opinions more because of some individuals in their networks than because of media or advertising: the influence of the physicians' social networks is major to make them adopt a new drug. [15,16] Pharmaceutical companies hire KOLs at different stages of the drug development process, from clinical trials to promotion. [17,18] Typically, KOLs are physicians or researchers who are respected in their field and recognized for their work, such as broad members of professional medical associations. [18–22]

Major ties between leaders of professional medical associations and the pharmaceutical industry have recently been described in North America. [10,11] In France, these links had never been studied yet.

In this study we described the nature and evolution of gifts, agreements and remunerations perceived by key opinion leaders (KOL) and other physicians using the data from the Transparency in Healthcare database. We also grouped gifts, agreements and remunerations perceived by these KOL for each professional medical association they belong to.

METHODS

As per our protocol (registration number: osf.io/m8syh), we conducted a retrospective study of the financial relationships between industry and board members of the national professional medical associations publishing clinical practice guidelines.

Identifying professional medical associations

Professional medical associations were defined as any group of physicians who published clinical practice guidelines in France. One author (MC) built the list of eligible associations by cross-checking three different databases: the "Catalogue et index des sites médicaux de langue française" (CISMEF) [23]), "Le Parisien" review professional medical associations catalogue [24]) and the "Bibliothèque Médicale AF Lemanissier" (BMLweb) [25]). We included only national associations and excluded association titled as concerning "rare disease". Then, MC searched for those who had published at least one clinical practice recommendation in 2018 or 2019 using Google scholar, academic medical library of the general hospital of Le Mans and CISMEF.

Identifying Key Opinion Leaders

Using each professional medical association's website, MC identified between October 2018 and May 2020 all physicians who were board members.
KOL were defined as members of the association's board or governing council but not of sub-committees. KOL were identified by their name, medical specialty and city of practice, on the medical association website then if missing on google. Discrepancies and uncertainties were resolved by discussion with a second author (AB).

The Transparency in Healthcare database was downloaded on may 18, 2020 from the website EurosForDocs[26]. EurosForDocs is a tool inspired by the American website DollarsForDocs. EurosForDocs aims to help querying and understanding the Transparency in Healthcare database by cleaning and grouping payments by categories and beneficiaries. It also harmonizes the identification of doctors using their unique identification number in the National Healthcare Professional Registry : the "RPPS" (Répertoire Partagé des Professionnels de Santé). RPPS of the KOL were identified by AS from Health-Directory database and Transparency in Healthcare database. Uncertainties were resolved by manual inspection (MC).

Identifying and extracting payment details

By using the RPPS unique identification number, data on payments for the identified leaders[27] were extracted, using categories within the database: gifts, agreements and remunerations. We took into consideration the data from the date they were obligatory to declare: gifts from January 1, 2014 to December 31, 2019 and agreements and remunerations from January 1, 2017 to December 31, 2019.

"Gifts" include anything that is granted without consideration, in kind or in cash, directly or indirectly, of an amount greater than or equal to 10€ ($11,4) including taxes. "Remunerations" represent the payment by companies for work or services, of an amount greater than or equal to 10€. "Conventions" are agreements involving obligations on both sides: participation in a congress, research or clinical trial activity, training action, etc. The characteristics and date from where the payments were mandatory to declare are presented in **table 1.**

< PLEASE INSERT TABLE 1 HERE >

Outcome measures and descriptive analyses

The primary outcome was the total amount of gifts received by all the medical physicians and by the identified KOL, year by year since 2014.

A secondary outcome was the number and amount of the 2 additional categories of payments available after 2017 (i.e. agreements and remunerations), year by year since 2017.

Distribution of individual results of KOL pooled for each professional medical association is also presented. Quantitative data were described using median (inter-quartile range, IQR) rather than mean to be less biased by the influence of extreme observations. Binary outcomes were described using n (percentage). All analyses were performed using R. [28]

Changes to protocol

The secondary outcome including agreements and remunerations was not part of the protocol as these declarations were not mandatory before 2017. However, after having noted that remunerations represented more than 3 times the yearly amount of gifts, it was decided to include agreements and remunerations because we might have missed an important part of physicians-industry ties.

Then, as we identified some outliers with implausible amounts, it was likely that the database contained some errors (e.g. some gifts may have been reported in cents by the company

[outliers typically ending in two zeros]). It was therefore decided a posteriori to exclude amounts exceeding 100 000€ ($118 000) for a single payment. It corresponds to 35 extreme observations (34 in 2019, 1 in 2018, i.e. 0.0005% of the gifts) and 32m€ (4% of the total and 13% of 2019).

Patient and public involvement

Patients and public were involved throughout the French FORMINDEP association that aims to improve the independence of physicians' medical education. FORMINDEP's members (patients and physicians) kindly accepted to participate to the manuscript reviewing and editing. French CI3P organization (Patient and Public Partnership Innovation Center of the Faculty of Medicine of Nice) also accepted to participate to the manuscript reviewing and editing. Their comments enhanced the manuscript's quality, especially the discussion.

RESULTS

Participants

We identified 238 professional medical associations. 101 of them had produced clinical practice guidelines in 2018 and/or 2019 and two of them had no website or no board on their website. We identified 605 KOL, 548 of them were found on the Transparency in Healthcare database. The number of KOL in each professional medical association ranged from 1 to 12, with a median of 6. 12 KOL belonged to more than one professional medical association. The way KOL were identified is described by the figure 1 : Flowchart.

< PLEASE INSERT HERE FIG.1 : FLOWCHART >

Transparency in Healthcare public database

The database contained 6b€ ($7.1b) of ties over 8 years. Gifts represented 1.7b€, agreements represented 1.3b€ and remunerations represented 3b€. [26] Gifts, agreements and remuneration are presented below from the year in which they were consistently declared, that is respectively since 2014, 2017 and 2017.

Gifts (2014-2019)

For all physicians 7 354 492 gifts were declared for a total amount of 818m€ ($936m) from 2014 to 2019. The median amount for a gift was 46€ (IQR= 25-60, $54).
Most KOL (83%) had at least one gift declared from 2014 to 2019. KOL's gifts represented 0.68% of the number of all physicians' gifts and 1.5% of the total amount of gifts, i.e. 12.3m€ ($14m). It represents a median of €3 700 of gifts per KOL per year. The median amount for a KOL's gift was 60€ (IQR = 30–214).

Overall, the gifts declared to all physicians decreased in number and value from 1.3m gifts (151m€) to 923 000 gifts (108m€).

The number, value and proportion of gifts declared to KOL decreased from 9 687 gifts (0.70% of the total number of gifts to physicians) / 2.2m€ (1.5% of the total value of gifts to physicians) to 6044 gifts (0.65% of the total number of gifts to physicians) / 1.5m€ (1.4% of the total value of gifts to physicians).

The evolution year by year for each specific category of gift from 2014 to 2019 is presented in **Table 2**.

< PLEASE INSERT HERE TABLE 2 >

Almost all (99%) associations had at least one member of its board who had at least one declared gift since 2014. The median amount of gifts declared for all the corresponding KOL of a professional medical association was 61 000€ (IQR= 14 000-143 000 ; $70 000) but varied widely between associations. 1% of the associations had no gift declared for their KOL, 16% had less than 1 000€ gifts per year for their KOL. 39% had between 10 000€ and 50 000€ gifts and 11% had more than 50 000 € gifts declared for their KOL each year.

Agreements (2017-2019)

Concerning non-KOL physicians, 1.67 millions agreements were declared for a total of 125m€ ($143m) from 2017 to 2019. There were 1.28 millions agreements (77%) for which the reported amount was null. A null amount can be explained either by a report in one of the two other categories (when the agreement is linked with a gift or remuneration), or by a wrong declaration.

KOL's agreements represented 0.72% of all agreements declared to physicians and 2.5% of the value of these agreements, i.e. 3m€ ($3,6m). It represents a median of €1 900 of declared agreements per KOL per year. There were 9 496 KOLs' agreements (79%) for which the reported amount was null.

Overall, agreements declared to all physicians were increasing from 42m€ in 2017 to 43m€ in 2019.

The evolution year by year of the total amount, and median amount of agreements is presented in **table 3**.

< PLEASE INSERT TABLE 3 HERE >

The number, the value and the proportion of agreements declared to KOL decreased each year, from 4 400 agreements (0.78% of the number of agreements to physicians) / 1.1m€ (2.6% of the value of agreements to physicians) in 2017 to 3 500 agreements (0.64% of the number of agreements to physicians) / 1m€ (2.3% of the value of agreements to physicians) in 2019. This evolution is depicted in **Figure 2.**

< PLEASE INSERT FIGURE 2 HERE >

The median amount of agreements declared to all the corresponding KOL of an association was 15 900€ per year (IQR= 390 to 35 617).

Remunerations (2017-2019)

For all physicians, 250 873 remunerations were declared totaling 156m€ ($178m) from 2017 to 2019. The median amount for a remuneration was 250€ (IQR 55-742) ($296). KOLs' perceived 2.3% of physicians' remunerations, i.e. 6.8m€ ($7.8m) or 4.4% of the total value of remunerations to physicians. Overall, KOLs received 4 times more remunerations than other physicians, which represents a median of €4 100 of remunerations per KOL per year.

Regarding all physicians, remunerations increased in number and total value but the median amount decreased sharply. The evolution of the total amount of remunerations is presented in **table 3.** Physicians' remunerations increased from 77 277 remunerations / 49m€ in 2017 to 96 160 remunerations / 54m€ in 2019.

The number, value and proportion of remunerations declared to KOL decreased each year from 2017 (1 900 remunerations, 2.5% of the number of remunerations to physicians, accounting for 2.3m€ and 4.8% of the value of remunerations to physicians) to 2019 (1 800 remunerations, 1.9% of the number of remunerations to physicians, accounting for 2.1m€ and 4% of the value of remunerations to physicians in 2019).

The median amount of remunerations declared for all the corresponding KOL of an association was 21 000€ per year (IQR 1012 - 68 977, $25 000).

DISCUSSION

Principle findings

During this period, 818m€ of gifts, 125m€ of agreements and 156m€ of remunerations were declared to physicians in France. The amount of gifts decreased and the total amount of declared agreements and remunerations increased. Gifts represented the largest amount declared.

Almost every professional medical association included at least one KOL who received one or more gifts since 2014 (99%) or 2017 (97%). Over the whole period, the median amount of gifts per association was €61 000 ($70 000). From 2017 to 2019, the median cumulative amount for each professional medical association was 15 900€ of agreements and 21 900€ of remunerations. The number and amount of gifts varied widely from one association to another, ranging from €0 to 160 000€ ($189 000) for all the members of one association on the studied period.

The number, value and proportion of gifts, agreements and remunerations for KOLs were slightly decreasing over time. Remunerations represented the largest amount declared to KOLs with a median amount per capita 4 times higher than for other physicians. KOLs represented 0.24% of the physicians but were associated to 1.5% of the gifts, 2.4% of the agreements and 4.4% of the remunerations in value. It represents €3 700 of gifts, €1 900 of agreements and €4 100 of remunerations per capita per year. This amount of agreements is probably underestimated since 79% of KOLs' agreements amount was declared null in the database (see above).

Strengths and Limitations

This study is exhaustive of all ties declared on the French Transparency in Healthcare database. All physicians practicing in France were included since ties are mandatory to declare.

However, the statements may be underestimated since many agreement's amounts were not available. Indeed, when a physician signs an agreement conferring an advantage, the amount can be declared either nil, in agreement, in gift or both in agreement and gift. There is no government control at this level.

The effect of this bias is difficult to predict : on the one hand, firms did not declare the amounts of thousands of agreements, thus underestimating the amounts received by physicians. On the other hand, the amount of an agreement could be double counted. The entire Eurofordocs database (with all beneficiaries, without time limitations) contains 5.5 million agreements, 3.3 million of which have a nil amount. 2.2 million gifts claim to be linked to an agreement, but have an invalid textual link. There are therefore at least 1.1 million agreements with a nil amount despite the legal obligation to declare it.

Another limitation lies in the fact that the data comes from the declarations of the pharmaceutical industry itself with typos. Moreover, there may be a delay in data reporting, and remunerations may have been misclassified as it was possible to declare them as gifts or as remunerations until October, 2017.

Finally, in the absence of an official definition, we choose an objective but restrictive definition of KOL which lead us to rule out many individuals of great leverage that could also be called KOL .

Comparison with other studies

Our results are in line with those observed worldwide but adds new data regarding the French context. Very recent U.S. study showed that nearly three-quarters of the executives of the 10 most influential professional medical associations in the U.S. had ties with the pharmaceutical industry, with wide variations in the amount of payments reported between the professional medical associations. [10] Total general payments of $24.8m (20.8m€, £18.9m) were linked to the 235 KOL of the 10 most influential professional medical associations in 3 years. The total median general payment was $6 000 (IQR $309 to $54 000) (5000€, £4 500).

In this study, KOLs received 10 times more per capita per year in total amount than the French KOLs, and more than 83 times more in terms of median amount.

The amount of money involved in this American study seems to be much more important. This difference could be explained by societal differences but also by the fact that we included professional medical associations regardless of their size, cost or influence. On the other hand, this difference can be explained by the fact that USA represents a population 5 times larger and 4 times more physicians, which may constitutes an important return on investments. Finally, in the US, there are more mandatory payments to report, and there are enforcement measures and effective penalties.[29]

Implications of this study

Despite multiple calls for more distance,[10,30–33] KOL have still privileged relationships with pharmaceutical industry. This phenomenon can lead to lower guidelines' quality and to a general loss of confidence in both KOL and physicians. Indeed, several guidelines were abrogated since there have been doubts about the independence of the experts involved in their writing. [34–37] In turn, Chakroun et al. have shown that conflict of interests disclosure reduces public and physicians' trust in KOL.[38] Experience shows that financial ties can also be instrumentalized to discredit any expert position, the link being used as an argument to call into question the scientific opinion. [39–41]

Our study's finding of remaining concealment of the agreements amounts, despite the legal obligation to declare them, shows that transparency is still in progress and that both researchers and citizens do not yet have access to all data. For us, the main area for improvement would be to make it mandatory to report the amount of benefits and remunerations conferred by the agreement in the agreement section. Moreover, the declarations should be checked by the public authorities, which is the only guarantee of the reliability of the information provided.

Future research might focus on the correlation between the amount of gifts and the medical specialty or the cost of the concerned diseases. Further research is needed to identify other kinds of KOL such as the department heads of the teaching hospitals, and the medical university lecturers. Financial ties could be tracked over time, acting as a nudge to help chart moves towards independence.

Acknowledgments

We thank Pierre-Alain Jachiet for his proofreading of the manuscript, his help to fully understand the database and use properly EurosForDocs.

Patients and public were involved throughout the French FORMINDEP association that aims to improve the independence of physicians' medical education. FORMINDEP's members (patients and physicians) kindly accepted to participate to the manuscript reviewing and editing. French CI3P organization (Patient and Public Partnership Innovation Center of the Faculty of Medicine of Nice) also accepted to participate to the manuscript reviewing and editing. Their comments enhanced the manuscript's quality, especially the discussion.

Footnotes

Funding : none

Competing interest : All authors have completed the ICMJE uniform disclosure form and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Author Contributions : MC and AB initiated and designed the study, searched the literature, interpreted the results and wrote the manuscript. AS performed the analysis, contributed to the study design and interpreted results. FN contributed to the study design and interpreted the results. AB is the garantor. All authors have critically revised the manuscript and approved the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethical approval : the French Commission Nationale Informatique et Libertés approved this study.

Data sharing statement : Data from EurosForDocs are available on https://www.eurosfordocs.fr/data#donn-es. Analytic code from the study is available on https://osf.io/4756p/?view_only=df16d649d87847e5aa9478960620bf81

The guarantor (AB) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspect of the study was omitted; and that any discrepancies from the study as originally planned have been explained.

Figures legend/Caption :

Figure 1. Flowchart, representing how KOL were identified by crossing three databases.

Figure 2. Evolution of the 3 kinds of financial ties for KOL and all physicians. The gifts declared to all physicians were decreasing in number and value over time; the number, the value and the proportion of gifts declared to KOL were decreasing. The agreements declared to all physicians were increasing; the number, the value and the proportion of agreements declared to KOL were decreasing. The remunerations declared to all physicians were increasing; the number, the value and the proportion of remunerations declared to KOL were decreasing.

References

1. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2017;2:MR000033. doi:10.1002/14651858.MR000033.pub3
2. Brunt CS. Physician characteristics, industry transfers, and pharmaceutical prescribing: Empirical evidence from medicare and the physician payment sunshine act. Health Serv Res. Published online October 1, 2018. doi:10.1111/1475-6773.13064

3. Hadland SE, Rivera-Aguirre A, Marshall BDL, Cerdá M. Association of Pharmaceutical Industry Marketing of Opioid Products With Mortality From Opioid-Related Overdoses. JAMA Netw Open. 2019;2(1):e186007. doi:10.1001/jamanetworkopen.2018.6007
4. DeJong C, Aguilar T, Tseng C-W, Lin GA, Boscardin WJ, Dudley RA. Pharmaceutical Industry–Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries. JAMA Intern Med. 2016;176(8):1114. doi:10.1001/jamainternmed.2016.2765
5. Goupil B, Balusson F, Naudet F, et al. Association between gifts from pharmaceutical companies to French general practitioners and their drug prescribing patterns in 2016: retrospective study using the French Transparency in Healthcare and National Health Data System databases. The BMJ. 2019;367. doi:10.1136/bmj.l6015
6. Schott G, Dünnweber C, Mühlbauer B, Niebling W, Pachl H, Ludwig W-D. Does the Pharmaceutical Industry Influence Guidelines? Dtsch Ärztebl Int. 2013;110(35-36):575-583. doi:10.3238/arztebl.2013.0575
7. Horn J, Checketts JX, Jawhar O, Vassar M. Evaluation of Industry Relationships Among Authors of Otolaryngology Clinical Practice Guidelines. JAMA Otolaryngol Neck Surg. 2018;144(3):194-201. doi:10.1001/jamaoto.2017.2741
8. Combs TR, Scott J, Jorski A, Heavener T, Vassar M. Evaluation of Industry Relationships Among Authors of Clinical Practice Guidelines in Gastroenterology. JAMA Intern Med. 2018;178(12):1711-1712. doi:10.1001/jamainternmed.2018.4730
9. Checketts JX, Sims MT, Vassar M. Evaluating Industry Payments Among Dermatology Clinical Practice Guidelines Authors. JAMA Dermatol. 2017;153(12):1229-1235. doi:10.1001/jamadermatol.2017.3109
10. Moynihan R, Albarqouni L, Nangla C, Dunn AG, Lexchin J, Bero L. Financial ties between leaders of influential US professional medical associations and industry: cross sectional study. BMJ. 2020;369. doi:10.1136/bmj.m1505
11. Elder K, Turner KA, Cosgrove L, et al. Reporting of financial conflicts of interest by Canadian clinical practice guideline producers: a descriptive study. Can Med Assoc J. 2020;192(23):E617. doi:10.1503/cmaj.191737
12. LOI N° 2011-2012 Du 29 Décembre 2011 Relative Au Renforcement de La Sécurité Sanitaire Du Médicament et Des Produits de Santé.; 2011.
13. Décret n° 2016-1939 du 28 décembre 2016 relatif à la déclaration publique d'intérêts prévue à l'article L. 1451-1 du code de la santé publique et à la transparence des avantages accordés par les entreprises produisant ou commercialisant des produits à finalité sanitaire et cosmétique destinés à l'homme | Legifrance. Accessed June 14, 2020. https://www.legifrance.gouv.fr/eli/decret/2016/12/28/AFSX1637582D/jo/texte
14. Fabbri A, Santos Ancel la, Mezinska S, Mulinari S, Mintzes B. Sunshine Policies and Murky Shadows in Europe: Disclosure of Pharmaceutical Industry Payments to Health Professionals in Nine European Countries. Int J Health Policy Manag. 2018;7(6):504-509. doi:10.15171/ijhpm.2018.20
15. Sismondo S. How to make opinion leaders and influence people. CMAJ Can Med Assoc J. 2015;187(10):759-760. doi:10.1503/cmaj.150032
16. Coleman J, Katz E. The Diffusion of an Innovation among Physicians! :18.
17. The Pharma Marketing Glossary. Pharma Marketing Network. Accessed July 19, 2020. https://www.pharma-mkting.com/glossary/
18. Moynihan R. Key opinion leaders: independent experts or drug representatives in disguise? BMJ. 2008;336(7658):1402-1403. doi:10.1136/bmj.39575.675787.651
19. Sismondo S. Key Opinion Leaders and the Corruption of Medical Knowledge: What the Sunshine Act Will and Won't Cast Light on. J Law Med Ethics. 2013;41(3):635-643. doi:10.1111/jlme.12073

20. Meffert JJ. Key opinion leaders: where they come from and how that affects the drugs you prescribe. Dermatol Ther. 2009;22(3):262-268. doi:10.1111/j.1529-8019.2009.01240.x
21. Revue Prescrire. Leaders d'opinion : coûteux, mais rentables pour les firmes pharmaceutiques. 2005;25(266):777.
22. Revue Prescrire. Les leaders d'opinion, instrument marketing des firmes. Rev Prescrire. 2012;32(341):219.
23. Société savante - CISMeF. Accessed June 14, 2020. http://www.chu-rouen.fr/page/cismef-type-ressource/societe-savante
24. Liste de sociétés savantes scientifiques en France. Accessed June 14, 2020. http://dictionnaire.sensagent.leparisien.fr/LISTE%20DE%20SOCIETES%20SAVANTES%20SCIENTIFIQUES%20EN%20FRANCE/fr-fr/
25. Nouveautés, consensus et lignes directrices - Bmlweb. Accessed June 14, 2020. http://www.bmlweb.org/nouveaute.html
26. Euros for Docs - vison par professionnel bénéficiaire. Accessed June 14, 2020. https://www.eurosfordocs.fr/metabase/dashboard/2
27. Traitement des données EurosforDocs. Euros For Docs. Accessed June 14, 2020. https://www.eurosfordocs.fr/data/
28. R Development Core Team (2005). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL: http://www.R-project.org. Accessed August 12, 2020. https://wp.unil.ch/asi/documentation/citer-r-dans-un-rapport/
29. Rapport : La prévention des conflits d'intérêts en matière d'expertise sanitaire – mars 2016. Accessed August 5, 2020. https://www.ccomptes.fr/sites/default/files/EzPublish/20160323-prevention-conflits-interets-en-matiere-expertise-sanitaire.pdf#page=65
30. Fava GA. Should the drug industry work with key opinion leaders? No. BMJ. 2008;336(7658):1405. doi:10.1136/bmj.39541.731493.59
31. Sculier J-P. Conflits d'intérêt : une notion souvent (volontairement) ignorée des médecins Conflicts of interest : a concept often (voluntary) ignored by physicians. Rev Med Brux. 2010;(31):199-205.
32. Wilson M. The Sunshine Act: Commercial conflicts of interest and the limits of transparency. Open Med. 2014;8(1):e10-e13.
33. Moynihan R, Bero L, Hill S, et al. Pathways to independence: towards producing and using trustworthy evidence. BMJ. 2019;367. doi:10.1136/bmj.l6576
34. Décision n°2011.05.064/MJ du 18 mai 2011 du Collège de la Haute Autorité de Santé portant abrogation de la recommandation « Diagnostic et prise en charge de la maladie d'Alzheimer et des maladies apparentées ». Haute Autorité de Santé. Accessed November 9, 2020. https://webzine.has-sante.fr/jcms/c_1056866/fr/decision-n2011-05-064/mj-du-18-mai-2011-du-college-de-la-haute-autorite-de-sante-portant-abrogation-de-la-recommandation-diagnostic-et-prise-en-charge-de-la-maladie-d-alzheimer-et-des-maladies-apparentees
35. Dyslipidémies : face au doute sur l'impartialité de certains de ses experts, la HAS abroge sa recommandation. Haute Autorité de Santé. Accessed August 5, 2020. https://www.has-sante.fr/jcms/c_2885402/fr/dyslipidemies-face-au-doute-sur-l-impartialite-de-certains-de-ses-experts-la-has-abroge-sa-recommandation
36. Traitement médicamenteux du diabète de type 2 : recommandation retirée le 2 mai 2011. Haute Autorité de Santé. Accessed August 5, 2020. https://www.has-sante.fr/jcms/c_459270/fr/traitement-medicamenteux-du-diabete-de-type-2-recommandation-retiree-le-2-mai-2011
37. Barbaroux A, Jedat V. Lifelong continuing education. Critical analysis of scientific and medical information. Management of links of interest. exercer 2020;163:233-6.

38. Chakroun R, Milhabet I. Medical opinion leaders conflict of interests: effects of disclosures on the trust of the public and general practitioners. Rev Epidemiol Sante Publique. 2011;59(4):233-242. doi:10.1016/j.respe.2010.12.011
39. Conflits d'intérêts : Karine Lacombe répond à Didier Raoult. egora.fr. Published June 26, 2020. Accessed August 5, 2020. https://www.egora.fr/actus-pro/sante-publique/59825-conflits-d-interets-karine-lacombe-repond-a-didier-raoult
40. Girard E. 118.000 euros de MSD, 116.000 euros de Roche : faut-il s'inquiéter des liens entre labos et conseils scientifiques ? Marianne. Published April 3, 2020. Accessed August 5, 2020. https://www.marianne.net/societe/118000-euros-de-msd-116000-euros-de-roche-faut-il-s-inquieter-des-liens-entre-labos-et
41. Sallet F, Lebossé V, Toulemonde M. #TransparenceCHU : comment nous avons enquêté sur les liens entre labos et médecins. leparisien.fr. Published January 10, 2020. Accessed August 6, 2020. https://www.leparisien.fr/economie/transparencechu-comment-nous-avons-enquete-sur-les-liens-entre-labos-et-medecins-10-01-2020-8233257.php

Table 1 presents the 3 categories of links of interest and the date from where they had to be declared on the Transparency in Healthcare database (base Transparence Santé). The Transparency in Healthcare database was laid down in the "Strengthening the safety of medicines and health products" law of December, 2011, and launched in July, 2014.

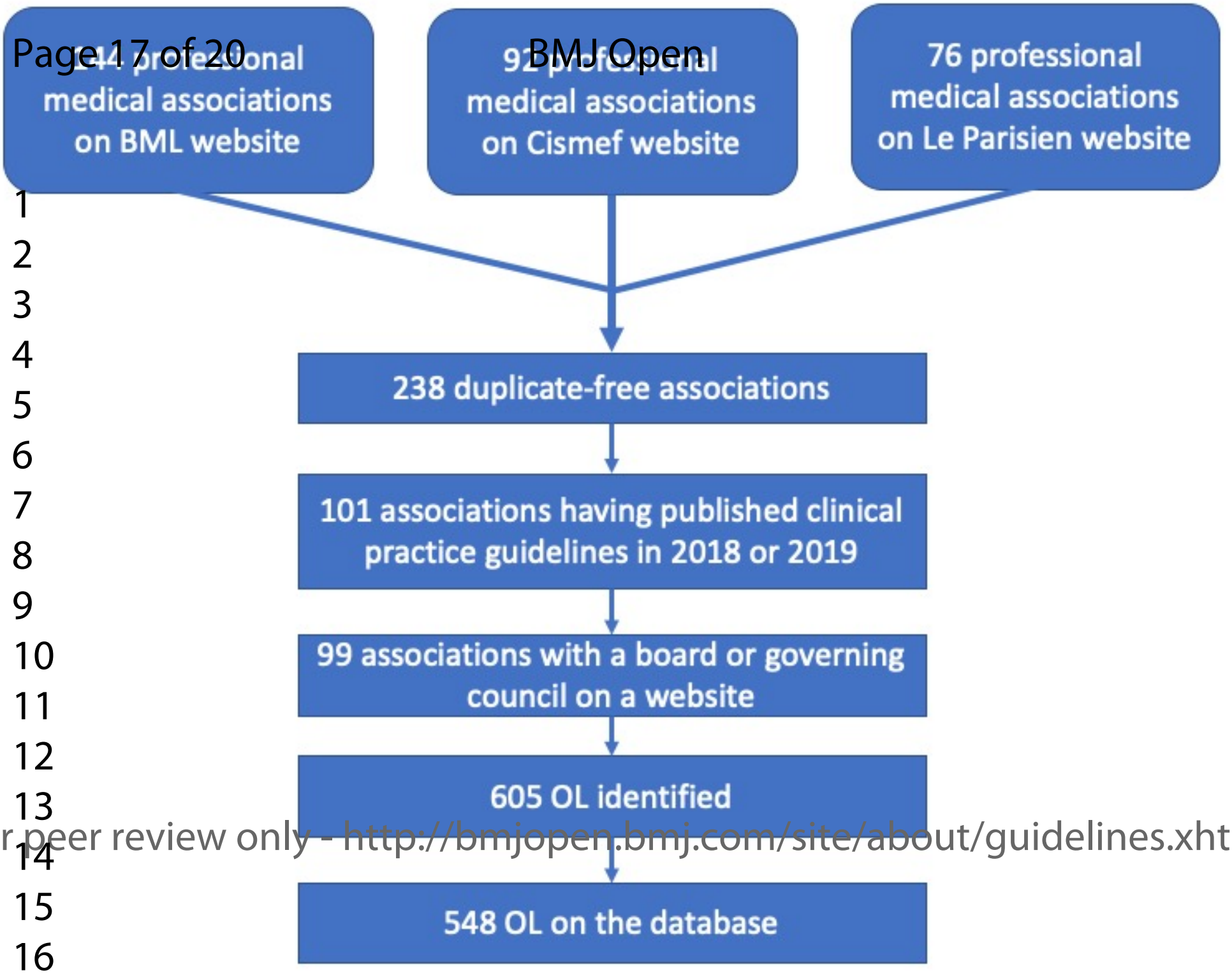
Type of ties	**Definition**	**Information mandatory to declare**
Gifts	Anything that is allocated or paid without consideration by a company to a health actor, with a value of more than 10 euros including taxes. Available categories on the website = gifts, contribution to the cost of promotional, scientific or professional events, accommodation, hospitality, catering, transport, transport and hospitality, in-kind donations, donations, donations of money, grants, training, expenditures for services and advice, fees, failed category association, empty, other.	Identity of the parties concerned, amount, nature and date of each benefit. Mandatory since the law of 2013; actual website availability in 2014.
Agreements	Contracts involving obligations on the part of the physician and the industry. For example, participation in a congress as a speaker (obligation fulfilled by the professional), with payment for transport and accommodation (obligation fulfilled by the company). The conventions concern research activities, clinical trials, participation in a scientific congress, training activities, etc.	Identity of the parties concerned, the organizer, the name, date and place of the event, date of the agreement, its precise purpose (mandatory since the law of 2013 ; actual website availability 2014) and the amount (mandatory since the law of 2016, actual website availability in 2017). If the agreements give rise to payments in benefits or remuneration, the payments can be indicated in the category agreements or in benefits or remuneration, with a numerical link to the agreement.
Remunerations	Payment for work or services with a value of more than 10 euros including taxes.	Identity of the parties, final beneficiary , date of payment, amount if it is greater than or equal to 10euros (available since 2015 but mandatory since the law of 2016, actual website availability in the remuneration section in 2017).

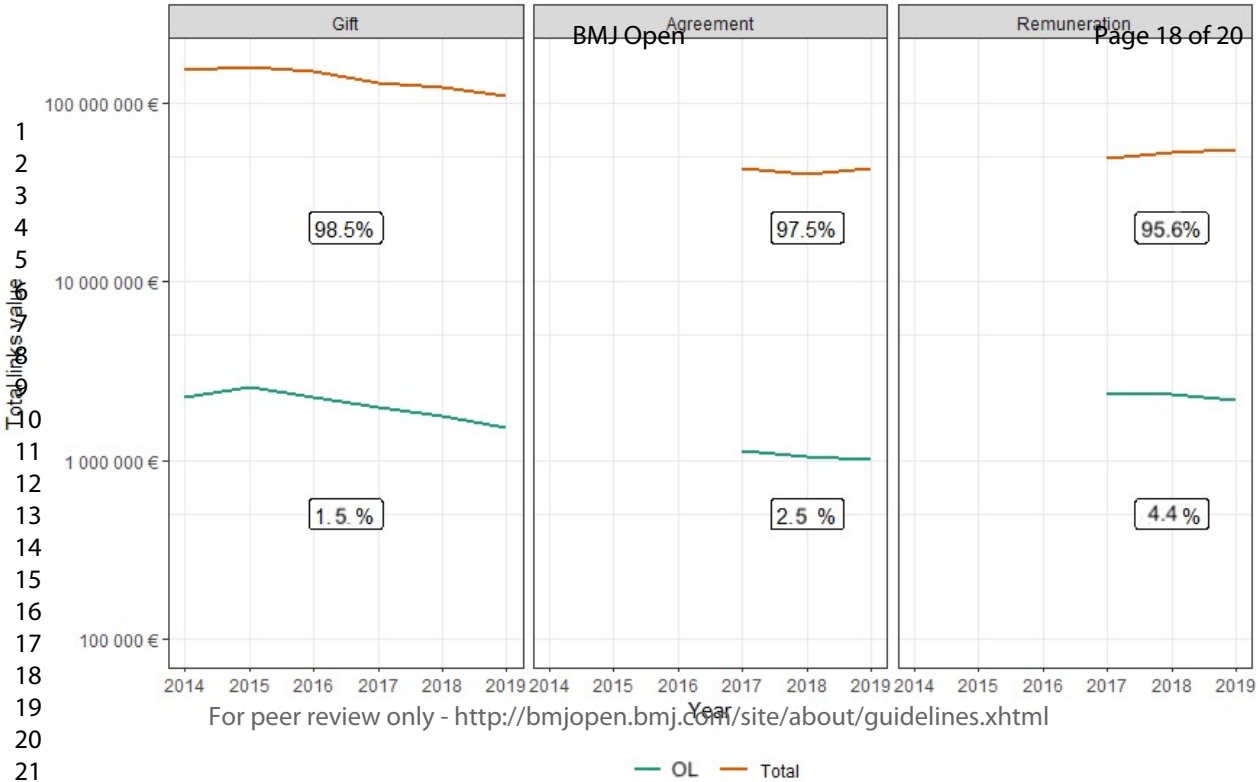
Table 2. Median (IQR) amount of gifts to KOL and non-KOL physicians in euros (€).

Gifts category	*Physicians category*	2014	2015	2016	2017	2018	2019
Accommodation	*All physicians*	210(165-314)	215 (165-341)	215 (170-314)	215 (164-323)	221 (170-349)	218 (173-328)
	KOL	218 (172-305)	220 (170-330)	218 (179-296)	226 (176-313)	221 (175-323)	229 (180-344)
Hospitality	*All physicians*	50 (27-118)	45 (25-60)	46 (24-60)	55 (30-60)	53 (28-60)	52 (28-60)
	KOL	70 (30-448)	58 (28.2-258)	60 (30-258)	80.5 (40-362)	60 (29-319)	60 (30-329)
Catering	*All physicians*	40 (24-55)	40 (24-56)	38 (23-55)	38 (23-56)	38 (23-56)	38 (24-57)
	KOL	40 (23-59)	40 (23-59)	40 (23-58)	40 (23-58)	40 (24-59)	40 (24-59)
Transport	*All physicians*	208 (91-420)	200 (88-398)	191 (85-380)	189 (79-357)	182 (81-344)	177 (77-332)
	KOL	202 (70-471)	206 (74.2-461)	244 (96-477)	207 (77-445)	198 (79.8-414)	187 (71-395)
Contributions to the cost of promotional events	*All physicians*	60 (50-400)	60 (50-404)	60 (44-400)	200 (55-455)	400 (250-590)	440 (260-650)
	KOL	320 (60-591)	350 (60-600)	390 (87-650)	450 (186-729)	470 (290-740)	538 (290-796)
Donations-Grants-Training	*All physicians*	21 (17-30)	23 (17-50)	36 (23-94)	62 (30-171)	55 (29-171)	55 (25-144)
	KOL	83 (60-275)	68 (27.5-1578)	96 (63.5-138)	76 (45-192)	155 (42-225)	80 (42-180)
Service and consulting	*All physicians*	26 (22-30)	30 (22-45)	30 (24-50)	30 (25-40)	50 (25-80)	116 (40-362)
	KOL	30 (24-120)	47 (29-325)	65 (30-600)	32 (25-83)	130 (74-309)	158 (69-506)
Other	*All physicians*	100 (30-350)	140 (30-496)	100 (19-375)	22 (16-84)	25 (16-104)	49 (16-220)
	KOL	337 (34.8-1000)	800 (195-1188)	700 (100-1000)	310 (23-915)	40 (12-153)	79.5 (12-500)
TOTAL	*All physicians*	45 (25-60)	45 (25-60)	45 (25-60)	46 (25-60)	48 (25-60)	49 (26-60)
	KOL	59 (29-198)	60 (30-224)	60 (30-217)	60 (30-213)	60 (31-214)	60 (31-210)

Table 3. Total amount, and median (IQR) amount of agreements, total and median (IQR) amount of remunerations to KOL and non-KOL physicians, year by year since they are consistently declared.

Payment category	Physicians category	Amount	2017	2018	2019	Total
Agreements	*All physicians*	Number of agreements for which the amount could not be found in the agreement section (percentage of the number of agreements)	446 204 (79%)	443 687 (79%)	394 393 (72%)	1 284 284
		Total value of agreements for which an amount could be found in the agreement section in €	42 905 877	39 962 079	43 098 150	125 966 106
		Number of agreements with a declared amount in the agreement section	118 860	119 844	150 987	389 691
	KOL	Number of agreements for which the amount could not be found in the agreement section (percentage of the number of agreements)	3 514 (80%)	3 319 (80%)	2 663 (76%)	9496
		Total value of agreements for which an amount could be found in the agreement section in €	1 123 947	1 040 295	1 000 651	3 164 893
		Number of agreements with a declared amount in the agreement section	903	837	843	2583
Remunerations	*All physicians*	Total amount in €	49 152 264	53 142 546	54 254 342	156 549 152
		Median (IQR)	300 (65-750)	350 (65-800)	130 (50-613)	250
		Number of remunerations	77 277	77 436	96 160	250 573
	KOL	Total amount in €	2 355 894	2 346 293	2 172 827	6 875 014
		Median (IQR)	946 (527-1440)	1000 (600-1497)	998 (538-1375)	1000
		Number of remunerations	1950	1901	1876	5718





Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	#4	Present key elements of study design early in the paper	3
Setting	#5	Describe the setting, locations, and relevant dates, including periods of	3

		recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	4
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	4
Bias	#9	Describe any efforts to address potential sources of bias	4
Study size	#10	Explain how the study size was arrived at	4
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	4
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	4
Statistical methods	#12c	Explain how missing data were addressed	4
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	4
Statistical methods	#12e	Describe any sensitivity analyses	4
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	5
Participants	#13b	Give reasons for non-participation at each stage	5
Participants	#13c	Consider use of a flow diagram	5

Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	5
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	5
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	5
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
Main results	#16b	Report category boundaries when continuous variables were categorized	5
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	5
Discussion			
Key results	#18	Summarise key results with reference to study objectives	7
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	7
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	7
Generalisability	#21	Discuss the generalisability (external validity) of the study results	7
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

BMJ Open

Sunshine on KOLs: Assessment of the nature, extent and evolution of financial ties between the leaders of professional medical associations and the pharmaceutical industry in France from 2014 to 2019: a retrospective study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051042.R1
Article Type:	Original research
Date Submitted by the Author:	25-Aug-2021
Complete List of Authors:	CLINCKEMAILLIE, Marie; Universite Cote d'Azur Faculte de Medecine, Département d'Enseignement et de Recherche en Médecine Générale, RETINES, HEALTHY SCANFF, Alexandre; Rennes 1 University Naudet, Florian; Rennes 1 University, Clinical Investigation Center (INSERM 1414) and Adult Psychiatry Department, Rennes University Hospital, Rennes, France BARBAROUX, Adriaan; Universite Cote d'Azur Faculte de Medecine, Département d'Enseignement et de Recherche en Médecine Générale, RETINES, LAPCOS, HEALTHY
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Ethics
Keywords:	ETHICS (see Medical Ethics), HEALTH ECONOMICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Public health < INFECTIOUS DISEASES

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Sunshine on KOLs:
Assessment of the nature, extent and evolution of financial ties between the leaders of professional medical associations and the pharmaceutical industry in France from 2014 to 2019: a retrospective study.

Marie CLINCKEMAILLIE, MD (ORCID: 0000-0001-6643-001X)[1], Alexandre SCANFF, MD (ORCID: 0000-0001-5419-817X)[2], Florian NAUDET, PhD (ORCID: 0000-0003-3760-3801)[2], Adriaan BARBAROUX, MD (ORCID: 0000-0002-9243-6922)[3].

[1]*Université Cote d'Azur, Département d'Enseignement et de Recherche en Médecine Générale, RETINES, HEALTHY, France*
[2]*Univ Rennes, CHU Rennes, Inserm, CIC 1414 [(Centre d'Investigation Clinique de Rennes)], F- 35000 Rennes, France*
[3] *Université Cote d'Azur, Département d'Enseignement et de Recherche en Médecine Générale, RETINES, LAPCOS, HEALTHY, France*

Corresponding author: A. Barbaroux
Adriaan.barbaroux@univ-cotedazur.fr; 2bis Avenue Durante, 06000 Nice

Word count of the manuscript text: 2985

ABSTRACT

Objective

To investigate the financial relationships between key opinion leader (KOL) or non-KOL physicians and pharmaceutical and device companies in France.

Design

Retrospective and descriptive study

Setting

All doctors practicing in France, with a focus on 548 KOLs (board members of the professional medical associations that published guidelines in 2018-2019, identified on the associations' websites between 2018 and 2020). Ties were collected from the "Transparency in Healthcare" database.

Main outcome measures

The number and the value of gifts from 2014 to 2019, and of remunerations and contractual agreements from 2017 to 2019.

Results

KOLs represented 0.24% of the total number of physicians in France. The total value of gifts declared in the French database for all physicians amounted to €818M ($936M, £741M). At least one gift was declared for 83% of KOLs. KOLs' gifts represented 0.68% of the total number of gifts to physicians and 1.5% of the total value of gifts, with a mean of €3,700 per capita per year.

The total value of contractual agreements declared for all physicians amounted to €125M. Contractual agreements involving the KOLs represented 0.72% of the number of contractual agreements with physicians and 2.5% of the value of the agreements, with a mean of €1,900 per capita per year.

A total of €156M in remunerations was declared for all physicians. KOL remunerations represented 2.3% of the number of physician remunerations and 4.4% of the total value of the remunerations paid to physicians, with a mean of €4,100 per capita per year.

Almost all professional medical associations (99%) had at least one KOL in their board with a financial tie to the industry, but the amount varied widely among the associations.

Conclusion

Financial relationships between KOLs and the industry in France are extensive. KOLs have much more financial ties than non-KOL practitioners.

Strengths and limitations of this study

- This is the first time the Transparency in Healthcare database was used to analyze the links between KOLs and the industry.
- The authors cross-checked the nationwide database of financial ties with three databases of professional medical associations.
- All medical doctors practicing in France were included, with a focus on 548 KOLs defined as board members of all the professional medical associations that published clinical practice guidelines in 2018 or 2019.
- The main limitation of this study arises from the quality of information provided by the French Transparency in Healthcare database.
- The definition of KOLs used here is somewhat restrictive and further research is needed to better understand the links between KOLs and the industry.

Keywords :
Conflict Of Interest – Key Opinion Leaders – public health – quality in health care – medical ethics

INTRODUCTION

Financial ties between healthcare workers and the pharmaceutical industry may affect every aspect of medical activity, from research to clinical practice.[1] Clinical trials and meta-analyses sponsored by the pharmaceutical industry are more likely to conclude that drugs are effective than non-sponsored trials.[2] Industry transfers of value to physicians have been shown to be associated with more expensive, more frequent and lower quality prescriptions.[3–6] Recommendations for clinical practice, which define diagnostic criteria and disease treatment, can also be influenced, since their authors often have ties with the industry.[7–13]

Following the example of the USA with the US Physician Payments Sunshine Act, France created the Transparency in Healthcare public database (transparence.santé.gouv.fr) in 2014.[14–16] Pharmaceutical and medical device industries are required by law to disclose the value of gifts, contractual agreements and remunerations they transfer to healthcare professionals in France. In this database, “Gifts” include anything that is granted without consideration, in kind or in cash, directly or indirectly, with a value greater than or equal to €10 ($11.4) including taxes. “Remunerations" represent the payment by companies for work or services with a value greater than or equal to €10. “Contractual agreements" involve obligations on both sides: participation in a congress, research or clinical trial activity, training action, etc. For more convenience, this paper will gather both pharmaceutical and medical device industries under the term “pharmaceutical industry”.

The term “Key Opinion Leaders” (KOLs) refers to physicians who influence their peers' medical practice, which includes but is not limited to prescribing behavior. It was coined by sociologists who demonstrated that people were more likely to change their opinions under the influence of individuals in their network than because of the media or advertising: physician social networks hold a major influence in making physicians adopt a new drug.[17,18] Pharmaceutical companies hire KOLs at different stages of the drug development process, from clinical trials to promotion.[19,20] Typically, KOLs are physicians or researchers who are respected in their field and recognized for their work, such as board members of professional medical associations.[20–24]

Major ties between the leaders of professional medical associations and the pharmaceutical industry have recently been described in North America.[11,12] In France, these financial ties had never been studied.

This paper uses the data from the Transparency in Healthcare database to describe the nature, the extent and the evolution of the financial ties of all physicians in France, with a focus on key opinion leaders (KOLs). The ties of professional medical associations were assessed by grouping the gifts, contractual agreements and remunerations received by the KOLs of each professional medical association.

METHODS

We conducted a retrospective study of the financial relationships between industry and the board members of national professional medical associations that publish clinical practice guidelines. As per our protocol (registration number: osf.io/m8syh), we took into consideration the financial ties of each KOL from 2014 to 2019. KOLs were defined as board members of an association from 2018 to 2020.

Identifying professional medical associations

Professional medical associations were defined as any group of physicians who publish clinical practice guidelines in France. One author (MC) built the list of eligible associations by

cross-checking three different databases: the "Bibliothèque Médicale AF Lemanissier" (BMLweb),[25] the "Catalogue et index des sites médicaux de langue française" (CISMEF),[26] and the "Le Parisien" catalogue of professional medical associations.[27] We included only national associations and excluded association titled as concerning a "rare disease". The BML website is an academic medical library that lists month by month all the consensus statements, guidelines and recommendations published in French. MC conducted a search through it from January 2018 to December 2019 and selected all the national professional medical associations regardless of the nature of the publications they were listed for. The next step was to examine the Cismef website, which has a "learned society" section that lists French speaking professional medical associations. MC selected all the professional medical associations in France from that list. Finally, MC used the "Le Parisien" database that lists French learned societies, and selected all the professional medical associations in the "medical science" section. Duplicates were then eliminated and MC examined the associations one by one to determine whether they had published guidelines in 2018 or 2019. To do so, BMLweb was used fist and then the search engine for clinical practice guidelines of the Cismef website if there was no match on BMLweb, and finally Google Scholar and the association website.

Identifying Key Opinion Leaders

Using each professional medical association's website, MC identified between October 2018 and May 2020 all the physicians who were board members.

KOLs were defined as members of the association's board or governing council but not of sub-committees. KOLs were identified by name, medical specialty and city of practice via the medical association website and if missing on Google. Discrepancies and uncertainties were resolved by discussion with a second author (AB).

The Transparency in Healthcare database was downloaded on May 18, 2020 from the EurosForDocs[28] website. EurosForDocs is a tool inspired by the American website DollarsForDocs. EurosForDocs aims to help browsers find and understand information in the Transparency in Healthcare database by cleaning and grouping payments by categories and beneficiaries. It also harmonizes the identification of doctors using their unique identification number in the National Healthcare Professional Registry: the "RPPS" (*Répertoire Partagé des Professionnels de Santé*). The RPPS of KOLs were identified by AS in the Health-Directory database and the Transparency in Healthcare database. Uncertainties were resolved by manual inspection (MC).

Identifying and extracting payment details

By using the RPPS unique identification number, data regarding payments to the identified leaders[29] were extracted using the database categories: gifts, contractual agreements and remunerations. We took the data into consideration starting from the date on which their declaration became mandatory: gifts from January 1, 2014 to December 31, 2019 and contractual agreements and remunerations from January 1, 2017 to December 31, 2019.

The characteristics and date on which declaration of the payments became mandatory are presented in **table 1.**

< PLEASE INSERT TABLE 1 HERE >

Outcome measures and descriptive analyses

The primary outcome was the total number and value of gifts received by all physicians and by the identified KOLs year by year since 2014.

A secondary outcome was the number and value of payments in the 2 additional categories available after 2017 (i.e. contractual agreements and remunerations) year by year since 2017.

The distribution of payments to individual KOLs grouped by professional medical association is also presented. Quantitative data were described using the median (inter-quartile range, IQR) rather than the mean to be less biased by extreme observations. Binary outcomes were described using n (percentage). All analyses were performed using R.[30]

Changes to protocol

The secondary outcome concerning contractual agreements and remunerations was not part of the protocol as these declarations were not mandatory before 2017. However, after having observed that the value of remunerations represented more than 3 times the yearly value of gifts, it was decided to include contractual agreements and remunerations because without them, an important part of physician-industry ties would have been missed.

We identified some outliers with implausible amounts which seemed to indicate that some of the information in the database contained errors (e.g. some gifts may have been reported in cents by the company [outliers typically ending in two zeros]). It was therefore decided a posteriori to exclude amounts exceeding €100,000 ($118,000) for a single payment. This corresponds to 35 extreme observations (34 in 2019, 1 in 2018, i.e. 0.0005% of the gifts) for an amount of €32M (4% of the total and 13% of 2019).

Patient and public involvement

Patients and public were involved through the French FORMINDEP association which aims to improve the independence of physicians' medical education. FORMINDEP members (patients and physicians) kindly accepted to participate by reviewing and editing the manuscript. The French CI3P organization (Patient and Public Partnership Innovation Center of the Faculty of Medicine of Nice) also accepted to participate in the manuscript's revision and editing. Their comments improved the manuscript's quality, especially the discussion.

RESULTS

Participants

We identified 238 professional medical associations. 101 of them had produced clinical practice guidelines in 2018 and/or 2019 and two of them had no website or did not describe their board on their website. We identified 605 KOLs. 548 of them were found on the Transparency in Healthcare database. The number of KOLs in each professional medical association ranged from 1 to 12, with a median of 6. 12 KOLs belonged to more than one professional medical association. The way KOLs were identified is described in the figure 1: Flowchart.

< PLEASE INSERT HERE FIG.1: FLOWCHART >

Transparency in Healthcare public database

The database reported financial ties totaling €6B ($7.1B) over 8 years. Gifts accounted for €1.7B, contractual agreements for €1.3B and remunerations for €3B.[28] Gifts, contractual agreements and remunerations are presented below starting from the year in which they were consistently declared, that is since 2014, 2017 and 2017 respectively.

Gifts (2014-2019)

When considering all physicians, 7,354,492 gifts were declared for a total value of €818M ($936M) from 2014 to 2019. The median value of a gift was €46 (IQR= 25-60, $54). For most KOLs (83%), at least one gift was declared from 2014 to 2019. Gifts to KOLs represented 0.68% of the total number of physician gifts and 1.5% of the total value of gifts, i.e. €12.3M ($14M). This corresponds to a mean of €3,700 in gifts per KOL per year. The median value of a KOL gift was €60 (IQR = 30–214, $71).

Overall, the gifts declared for all physicians decreased in number and value from 1.3M gifts (€151M) to 923,000 gifts (€108M).

The number, value and proportion of gifts declared for KOLs decreased from 9,687 gifts (0.70% of the total number of gifts to physicians) / €2.2M (1.5% of the total value of gifts to physicians) to 6,044 gifts (0.65% of the total number of gifts to physicians) / €1.5M (1.4% of the total value of gifts to physicians).

The evolution year by year for each specific category of gift from 2014 to 2019 is presented in **Table 2**.

< PLEASE INSERT HERE TABLE 2 >

Almost all (99%) associations had at least one board member for whom at least one gift had been declared since 2014. The median value of gifts declared for all the corresponding KOLs of a professional medical association was €61,000 (IQR= 14,000-143,000; $70,000) but varied widely between associations. For 1% of the associations, no gift had been declared for their KOLs. For 16%, gifts to their KOLs represented less than €1,000 per year. For 39%, the value of gifts ranged between €10,000 and €50,000 and for 11%, more than €50,000 had been declared in gifts to their KOLs each year.

Contractual agreements (2017-2019)

For all physicians, 1.67 million contractual agreements were declared from 2017 to 2019 for a total of €125M ($143M). For 1.28 million of these agreements (77%), the reported amount was null. A null amount can be explained either by a joint report in one of the two other categories (when the agreement is linked with a gift or remuneration) or by a wrong declaration.

Contractual agreements with KOLs represented 0.72% of all agreements declared for physicians and 2.5% of the value of these agreements, i.e. €3M ($3,6M). This corresponds to a mean of €1,900 in declared agreements per KOL per year. For 9,496 KOL agreements (79%), the reported amount was null.

Overall, contractual agreements declared for all physicians increased from €42M in 2017 to €43M in 2019.

The evolution year by year of the total value and median value of agreements is presented in **table 3**.

< PLEASE INSERT TABLE 3 HERE >

The number, the value and the proportion of contractual agreements declared for KOLs decreased each year, from 4,400 agreements (0.78% of the number of agreements with physicians) / €1.1M (2.6% of the value of agreements with physicians) in 2017 to 3,500 agreements (0.64% of the number of agreements with physicians) / €1M (2.3% of the value of agreements with physicians) in 2019. This evolution is depicted in **Figure 2.**

< PLEASE INSERT FIGURE 2 HERE >

The median value of contractual agreements declared for all the corresponding KOLs of an association was €15,900 per year and also varied widely between associations (IQR= 390 – 35,617).

Remunerations (2017-2019)

For all physicians, 250,873 remunerations were declared totaling €156M ($178M) from 2017 to 2019. The median amount of a remuneration was €250 (IQR 55-742) ($296). KOLs received 2.3% of physician remunerations, i.e. €6.8M ($7.8M) or 4.4% of the total value of remunerations to physicians. Overall, KOLs received 4 times more remunerations than other physicians, which represents a mean of €4,100 in remunerations per KOL per year.

Regarding all physicians, remunerations increased in number and total value but the median amount decreased sharply. The evolution of the total amount of remunerations is presented in **table 3.** Physician remunerations increased from 77,277 remunerations / €49M in 2017 to 96,160 remunerations / €54M in 2019.

The number, value and proportion of remunerations declared for KOLs decreased each year from 2017 (1,900 remunerations, 2.5% of the number of remunerations to physicians, accounting for €2.3M and 4.8% of the value of remunerations to physicians) to 2019 (1,800 remunerations, 1.9% of the number of remunerations to physicians, accounting for €2.1M and 4% of the value of remunerations to physicians in 2019).

The median amount of remunerations declared for all the corresponding KOLs of an association was €21,000 per year and also varied widely between associations (IQR 1012 - 68 977, $25,000).

DISCUSSION

Principle findings

From 2014 to 2019, €818M in gifts were declared for physicians in France. From 2017 to 2019, €125M in contractual agreements and €156M in remunerations were declared for physicians in France. The amount of gifts decreased while the total amount of declared contractual agreements and remunerations increased. Gifts represented the largest amount declared. 83% of the KOLs received at least one gift from the pharmaceutical industry from 2014 to 2019 for a total amount of €12.3M.

Almost every professional medical association included at least one KOL who had received one or more gifts since 2014 (99%) or 2017 (97%). Over the whole period, the median value of gifts per association was €61,000 ($70,000). From 2017 to 2019, the median cumulative value for each professional medical association was €15,900 in contractual agreements and €21,900 in remunerations. The number and value of gifts, contractual agreements and remunerations for all the members of a single association varied widely from one association to another.

The number, value and proportion of gifts, contractual agreements and remunerations for KOLs slightly decreased over time. Remunerations represented the largest amount declared for KOLs with a median amount per capita 4 times higher than for other physicians. KOLs represented 0.24% of the physicians but were associated with 1.5% of the gifts, 2.4% of the contractual agreements and 4.4% of the remunerations in value. This represents €3,700 in gifts, €1,900 in agreements and €4,100 in remunerations per capita per year. The amount for contractual agreements is probably underestimated since 79% of KOL agreement amounts were declared null in the database (see above).

Strengths and Limitations

This study is exhaustive of all ties declared in the French Transparency in Healthcare database. All physicians practicing in France were included since declaration of industry ties is mandatory.

However, the results may be underestimated since many amounts for contractual agreements were not available. One reason for this is that when a physician signs an agreement conferring an advantage, the amount can be declared nil as a contractual agreement or a gift, or declared as both an agreement and a gift. There is no government control at this level.

The effect of this bias is difficult to predict. Either firms did not declare the amount of thousands of contractual agreements, thus underestimating the amounts received by physicians or the amount of an agreement could have been counted twice. The entire Eurofordocs database (with all beneficiaries, without time limitation) contains 5.5 million contractual agreements, 3.3 million of which have a nil amount. 2.2 million gifts are reported to be linked to an agreement but have an invalid textual link. There are therefore at least 1.1 million contractual agreements with a nil amount despite the legal obligation to declare them.

Another limitation lies in the fact that the data comes from the declarations of the pharmaceutical industry itself with typos. Moreover, there may be a delay in data reporting, and remunerations may have been misclassified as it was possible to declare them as gifts or as remunerations until October, 2017.

Finally, in the absence of an official definition, we chose an objective but restrictive definition of a KOL which led us to rule out many individuals with great leverage who could also have been included as KOLs.

Comparison with other studies

Our results are in line with those observed worldwide but add new data regarding the French context. A very recent US study showed that nearly three-quarters of the leaders of the 10 most influential professional medical associations in the USA had ties with the pharmaceutical industry, with wide variations in the amount of payments reported between the professional medical associations.[11] Total general payments of $24.8M (€20.8M, £18.9M) were linked to the 235 KOLs of the 10 most influential professional medical associations over 3 years. The total median general payment was $6,000 (IQR $309 to $54 000) (€5,000, £4,500).

In the American study, KOLs received 10 times more per capita per year in total amount than the French KOLs, and more than 83 times more in terms of median amount.

The amounts involved in the American study seems to be much greater. This difference could be explained by societal differences but also by the fact that we included professional medical associations regardless of their size, cost or influence. The difference could also be explained by the fact that the USA has a population 5 times larger than France and has 4 times more physicians, which may represent an important return on investment. Finally, in the USA, there are more mandatory payments to report, and there are enforcement measures and effective penalties that do not exist in France.[31]

Implications of this study

Despite multiple calls for more distance,[1,11,32–34] KOLs still have privileged relationships with the pharmaceutical industry. This phenomenon can lead to lower quality in guidelines and to a general loss of confidence in both KOLs and physicians. In recent years, several guidelines have been abrogated due to doubts about the independence of the experts involved in writing them.[35–38] In turn, Chakroun et al. have shown that disclosure of conflicts of interest reduces public and physician trust in KOLs.[39] Experience shows that financial ties can also be instrumentalized to discredit any expert position, the link being used as an argument to call into question the scientific opinion.[40–42]

Our study's finding of remaining concealments in the amounts of contractual agreements, despite the legal obligation to declare them, shows that transparency is still in progress and that both researchers and citizens do not yet have access to all the data. For us, the main area for improvement would be to make it mandatory to report the amount of gifts and remunerations conferred by a contractual agreement in the contractual agreement section. In addition, the declarations should be checked by the public authorities, which is the only way to guarantee the reliability of the information provided.

Future research might focus on the correlation between the amount of gifts and the medical specialty or the cost of the relevant diseases. Further research is needed to identify other kinds of KOLs such as the department heads of teaching hospitals, and medical university lecturers. Financial ties could be tracked over time, acting as a nudge to help chart moves towards independence.

Acknowledgments

The authors thank Pierre-Alain Jachiet for his proofreading of the manuscript, his help to fully understand the database and properly use EurosForDocs.

Patients and public were involved through the French FORMINDEP association that aims to improve the independence of physicians' medical education. FORMINDEP members (patients and physicians) kindly accepted to participate by reviewing and editing the manuscript. The French CI3P organization (Patient and Public Partnership Innovation Center of the Faculty of Medicine of Nice) also accepted to participate in the manuscript's revision and editing. Their comments improved the manuscript's quality, especially the discussion.

The authors also thank the reviewers and the editor for valuable comments that helped to improve the manuscript and Yvonne van der Does (Office of International Scientific Visibility, Université Côte d'Azur) for proofreading.

The research team would like to thank the « Agence Régionale de Santé Provence Alpe Côté d'Azur » for funding the Article Processing Charges.

Footnotes

Funding: none

Competing interest: All authors have completed the ICMJE uniform disclosure form and declare: no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Author contributions: MC and AB initiated and designed the study, searched the literature, interpreted the results and wrote the manuscript. AS performed the analysis, contributed to the study design and interpreted results. FN contributed to the study design and interpreted the results. AB is the guarantor. All authors have critically revised the manuscript and approved the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethical approval: Ethics approval was unnecessary because of the non-pharmaceutical bio-medical nature of this research. Ethical aspects nevertheless respect the French legislation. The data protection officer of the general and teaching hospital of Nice approved this study.

Data sharing statement: Data from EurosForDocs are available on https://www.eurosfordocs.fr/data#donn-es. Analytic code from the study is available on https://osf.io/4756p/?view_only=df16d649d87847e5aa9478960620bf81

The guarantor (AB) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspect of the study was omitted; and that any discrepancies from the study as originally planned have been explained.

Figures legend/Caption:

Figure 1. Flowchart representing how KOLs were identified by cross-checking three databases.

Figure 2. Evolution of the 3 kinds of financial ties for KOLs and all physicians. The gifts declared for all physicians decreased in number and value over time; the number, the value and the proportion of gifts declared for KOLs decreased. The contractual agreements declared for all physicians increased; the number, the value and the proportion of contractual agreements declared for KOLs decreased. The remunerations declared for all physicians increased; the number, the value and the proportion of remunerations declared for KOLs decreased.

References

1. Moynihan R, Bero L, Hill S, et al. Pathways to independence: towards producing and using trustworthy evidence. *BMJ*. 2019;367. doi:10.1136/bmj.l6576
2. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev*. 2017;2:MR000033. doi:10.1002/14651858.MR000033.pub3
3. Brunt CS. Physician characteristics, industry transfers, and pharmaceutical prescribing: Empirical evidence from medicare and the physician payment sunshine act. *Health Serv Res*. Published online October 1, 2018. doi:10.1111/1475-6773.13064
4. Hadland SE, Rivera-Aguirre A, Marshall BDL, Cerdá M. Association of Pharmaceutical Industry Marketing of Opioid Products With Mortality From Opioid-Related Overdoses. *JAMA Netw Open*. 2019;2(1):e186007. doi:10.1001/jamanetworkopen.2018.6007
5. DeJong C, Aguilar T, Tseng C-W, Lin GA, Boscardin WJ, Dudley RA. Pharmaceutical Industry–Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries. *JAMA Intern Med*. 2016;176(8):1114. doi:10.1001/jamainternmed.2016.2765
6. Goupil B, Balusson F, Naudet F, et al. Association between gifts from pharmaceutical companies to French general practitioners and their drug prescribing patterns in 2016: retrospective study using the French Transparency in Healthcare and National Health Data System databases. *The BMJ*. 2019;367. doi:10.1136/bmj.l6015
7. Schott G, Dünnweber C, Mühlbauer B, Niebling W, Pachl H, Ludwig W-D. Does the Pharmaceutical Industry Influence Guidelines? *Dtsch Ärztebl Int*. 2013;110(35-36):575-583. doi:10.3238/arztebl.2013.0575
8. Horn J, Checketts JX, Jawhar O, Vassar M. Evaluation of Industry Relationships Among Authors of Otolaryngology Clinical Practice Guidelines. *JAMA Otolaryngol Neck Surg*. 2018;144(3):194-201. doi:10.1001/jamaoto.2017.2741
9. Combs TR, Scott J, Jorski A, Heavener T, Vassar M. Evaluation of Industry Relationships Among Authors of Clinical Practice Guidelines in Gastroenterology. *JAMA*

Intern Med. 2018;178(12):1711-1712. doi:10.1001/jamainternmed.2018.4730
10. Checketts JX, Sims MT, Vassar M. Evaluating Industry Payments Among Dermatology Clinical Practice Guidelines Authors. *JAMA Dermatol*. 2017;153(12):1229-1235. doi:10.1001/jamadermatol.2017.3109
11. Moynihan R, Albarqouni L, Nangla C, Dunn AG, Lexchin J, Bero L. Financial ties between leaders of influential US professional medical associations and industry: cross sectional study. *BMJ*. 2020;369. doi:10.1136/bmj.m1505
12. Elder K, Turner KA, Cosgrove L, et al. Reporting of financial conflicts of interest by Canadian clinical practice guideline producers: a descriptive study. *Can Med Assoc J*. 2020;192(23):E617. doi:10.1503/cmaj.191737
13. Moynihan RN, Cooke GPE, Doust JA, Bero L, Hill S, Glasziou PP. Expanding Disease Definitions in Guidelines and Expert Panel Ties to Industry: A Cross-sectional Study of Common Conditions in the United States. *PLoS Med*. 2013;10(8):e1001500. doi:10.1371/journal.pmed.1001500
14. *LOI N° 2011-2012 Du 29 Décembre 2011 Relative Au Renforcement de La Sécurité Sanitaire Du Médicament et Des Produits de Santé*.; 2011.
15. Décret n° 2016-1939 du 28 décembre 2016 relatif à la déclaration publique d'intérêts prévue à l'article L. 1451-1 du code de la santé publique et à la transparence des avantages accordés par les entreprises produisant ou commercialisant des produits à finalité sanitaire et cosmétique destinés à l'homme | Legifrance. Accessed June 14, 2020. https://www.legifrance.gouv.fr/eli/decret/2016/12/28/AFSX1637582D/jo/texte
16. Fabbri A, Santos Ancel la, Mezinska S, Mulinari S, Mintzes B. Sunshine Policies and Murky Shadows in Europe: Disclosure of Pharmaceutical Industry Payments to Health Professionals in Nine European Countries. *Int J Health Policy Manag*. 2018;7(6):504-509. doi:10.15171/ijhpm.2018.20
17. Sismondo S. How to make opinion leaders and influence people. *CMAJ Can Med Assoc J*. 2015;187(10):759-760. doi:10.1503/cmaj.150032
18. Coleman J, Katz E. The Diffusion of an Innovation among Physicians! :18.
19. The Pharma Marketing Glossary. Pharma Marketing Network. Accessed July 19, 2020. https://www.pharma-mkting.com/glossary/
20. Moynihan R. Key opinion leaders: independent experts or drug representatives in disguise? *BMJ*. 2008;336(7658):1402-1403. doi:10.1136/bmj.39575.675787.651
21. Sismondo S. Key Opinion Leaders and the Corruption of Medical Knowledge: What the Sunshine Act Will and Won't Cast Light on. *J Law Med Ethics*. 2013;41(3):635-643. doi:10.1111/jlme.12073
22. Meffert JJ. Key opinion leaders: where they come from and how that affects the drugs you prescribe. *Dermatol Ther*. 2009;22(3):262-268. doi:10.1111/j.1529-8019.2009.01240.x
23. Revue Prescrire. Leaders d'opinion : coûteux, mais rentables pour les firmes pharmaceutiques. 2005;25(266):777.
24. Revue Prescrire. Les leaders d'opinion, instrument marketing des firmes. *Rev Prescrire*. 2012;32(341):219.
25. Nouveautés, consensus et lignes directrices - Bmlweb. Accessed June 14, 2020. http://www.bmlweb.org/nouveaute.html
26. Société savante - CISMeF. Accessed June 14, 2020. http://www.chu-rouen.fr/page/cismef-type-ressource/societe-savante
27. Liste de sociétés savantes scientifiques en France. Accessed June 14, 2020. http://dictionnaire.sensagent.leparisien.fr/LISTE%20DE%20SOCIETES%20SAVANTES%20SCIENTIFIQUES%20EN%20FRANCE/fr-fr/
28. Euros for Docs - vison par professionnel bénéficiaire. Accessed June 14, 2020. https://www.eurosfordocs.fr/metabase/dashboard/2

29. Traitement des données EurosforDocs. Euros For Docs. Accessed June 14, 2020. https://www.eurosfordocs.fr/data/
30. R Development Core Team (2005). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL: http://www.R-project.org. Accessed August 12, 2020. https://wp.unil.ch/asi/documentation/citer-r-dans-un-rapport/
31. Rapport : La prévention des conflits d'intérêts en matière d'expertise sanitaire – mars 2016. Accessed August 5, 2020. https://www.ccomptes.fr/sites/default/files/EzPublish/20160323-prevention-conflits-interets-en-matiere-expertise-sanitaire.pdf#page=65
32. Fava GA. Should the drug industry work with key opinion leaders? No. *BMJ*. 2008;336(7658):1405. doi:10.1136/bmj.39541.731493.59
33. Sculier J-P. Conflits d'intérêt : une notion souvent (volontairement) ignorée des médecins Conflicts of interest : a concept often (voluntary) ignored by physicians. *Rev Med Brux*. 2010;(31):199-205.
34. Wilson M. The Sunshine Act: Commercial conflicts of interest and the limits of transparency. *Open Med*. 2014;8(1):e10-e13.
35. Décision n°2011.05.064/MJ du 18 mai 2011 du Collège de la Haute Autorité de Santé portant abrogation de la recommandation « Diagnostic et prise en charge de la maladie d'Alzheimer et des maladies apparentées ». Haute Autorité de Santé. Accessed November 9, 2020. https://webzine.has-sante.fr/jcms/c_1056866/fr/decision-n2011-05-064/mj-du-18-mai-2011-du-college-de-la-haute-autorite-de-sante-portant-abrogation-de-la-recommandation-diagnostic-et-prise-en-charge-de-la-maladie-d-alzheimer-et-des-maladies-apparentees
36. Dyslipidémies : face au doute sur l'impartialité de certains de ses experts, la HAS abroge sa recommandation. Haute Autorité de Santé. Accessed August 5, 2020. https://www.has-sante.fr/jcms/c_2885402/fr/dyslipidemies-face-au-doute-sur-l-impartialite-de-certains-de-ses-experts-la-has-abroge-sa-recommandation
37. Traitement médicamenteux du diabète de type 2 : recommandation retirée le 2 mai 2011. Haute Autorité de Santé. Accessed August 5, 2020. https://www.has-sante.fr/jcms/c_459270/fr/traitement-medicamenteux-du-diabete-de-type-2-recommandation-retiree-le-2-mai-2011
38. Barbaroux A, Jedat V. Lifelong continuing education. Critical analysis of scientific and medical information. Management of links of interest. exercer 2020;163:233-6.
39. Chakroun R, Milhabet I. Medical opinion leaders conflict of interests: effects of disclosures on the trust of the public and general practitioners. *Rev Epidemiol Sante Publique*. 2011;59(4):233-242. doi:10.1016/j.respe.2010.12.011
40. Conflits d'intérêts : Karine Lacombe répond à Didier Raoult. egora.fr. Published June 26, 2020. Accessed August 5, 2020. https://www.egora.fr/actus-pro/sante-publique/59825-conflits-d-interets-karine-lacombe-repond-a-didier-raoult
41. Girard E. 118.000 euros de MSD, 116.000 euros de Roche : faut-il s'inquiéter des liens entre labos et conseils scientifiques ? Marianne. Published April 3, 2020. Accessed August 5, 2020. https://www.marianne.net/societe/118000-euros-de-msd-116000-euros-de-roche-faut-il-s-inquieter-des-liens-entre-labos-et
42. Sallet F, Lebossé V, Toulemonde M. #TransparenceCHU : comment nous avons enquêté sur les liens entre labos et médecins. leparisien.fr. Published January 10, 2020. Accessed August 6, 2020. https://www.leparisien.fr/economie/transparencechu-comment-nous-avons-enquete-sur-les-liens-entre-labos-et-medecins-10-01-2020-8233257.php

Table 1 presents the 3 categories of financial ties and the date from which they had to be declared in the Transparency in Healthcare database (Transparence-Santé). The Transparency in Healthcare database was laid down in the "Strengthening the safety of medicines and health products" law of December, 2011, and launched in July, 2014.

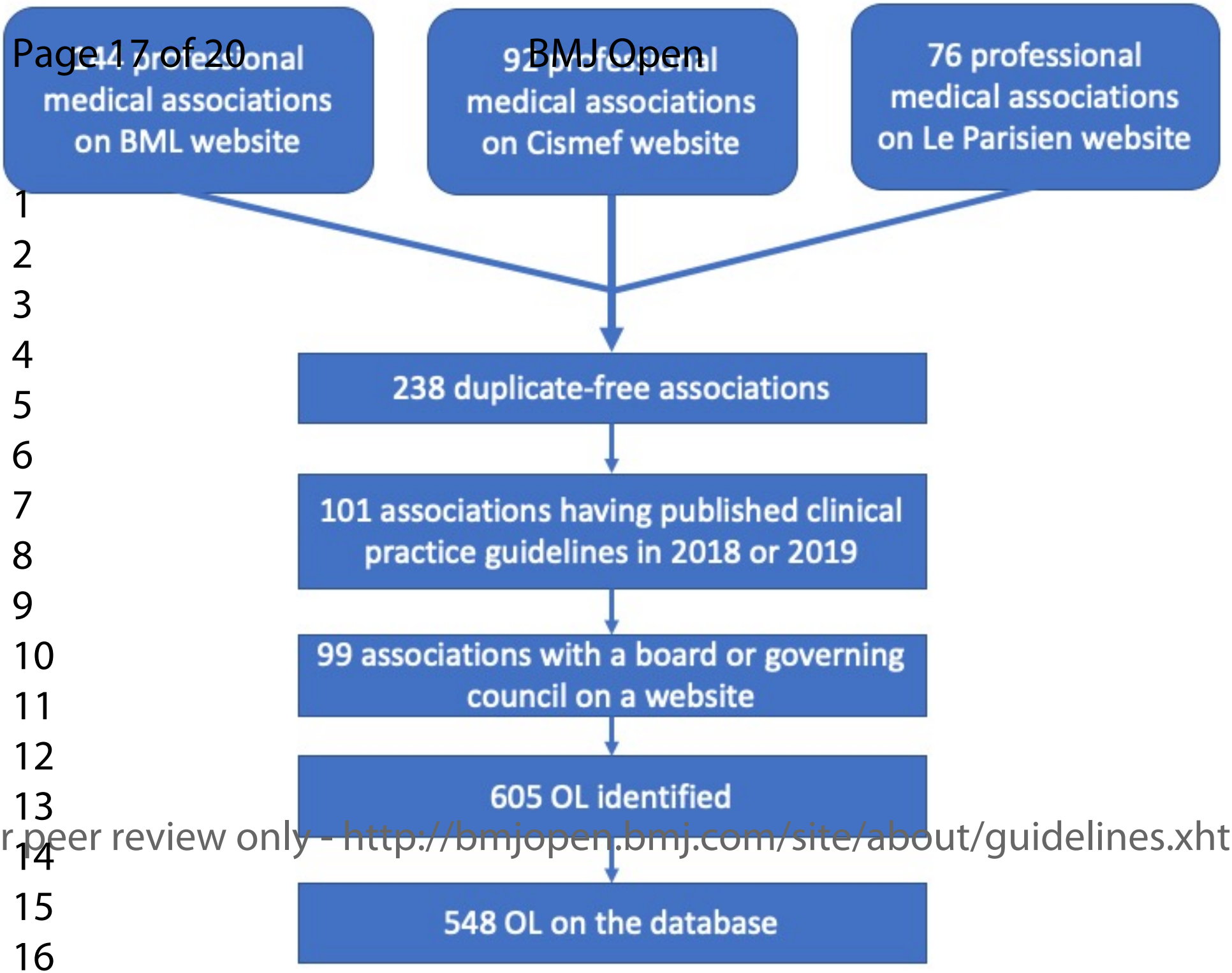
Type of ties	**Definition**	**Mandatory information to declare**
Gifts	Anything that is allocated or paid without consideration by a company to a health actor, with a value greater than or equal to 10 euros including taxes. Available categories on the website = gifts, contribution to the cost of promotional, scientific or professional events, accommodation, hospitality, catering, transport, transport and hospitality, in-kind donations, donations, donations of money, grants, training, expenditures for services and advice, fees, failed category association, empty, other.	Identity of the parties concerned, amount, nature and date of each gift. Mandatory since the law of 2013; actual website availability in 2014.
Contractual Agreements	Contracts involving obligations on the part of the physician and the industry. For example, participation in a congress as a speaker by the physician with payment for the lecture by the company, or participation at the presentation of a new medical device by the physician with payment for transport and accommodation by the company. The agreements concern research activities, clinical trials, participation in a scientific congress or training activities.	Identity of the parties concerned, the organizer, the name, date and place of the event, date of the agreement, its precise purpose (mandatory since the law of 2013; actual availability on the website since 2014) and the amount (mandatory since the law of 2016, actual availability on the website since 2017). If the agreements give rise to payments in gifts or remuneration, the payments can be reported in the agreements category or the gifts or remunerations categories, with a numerical link to the agreement.
Remunerations	Payment for work or services with a value of more than 10 euros including taxes.	Identity of the parties, final beneficiary, date of payment, amount if it is greater than or equal to 10 euros (available since 2015 but mandatory since the law of 2016, actual website availability in the remuneration section in 2017).

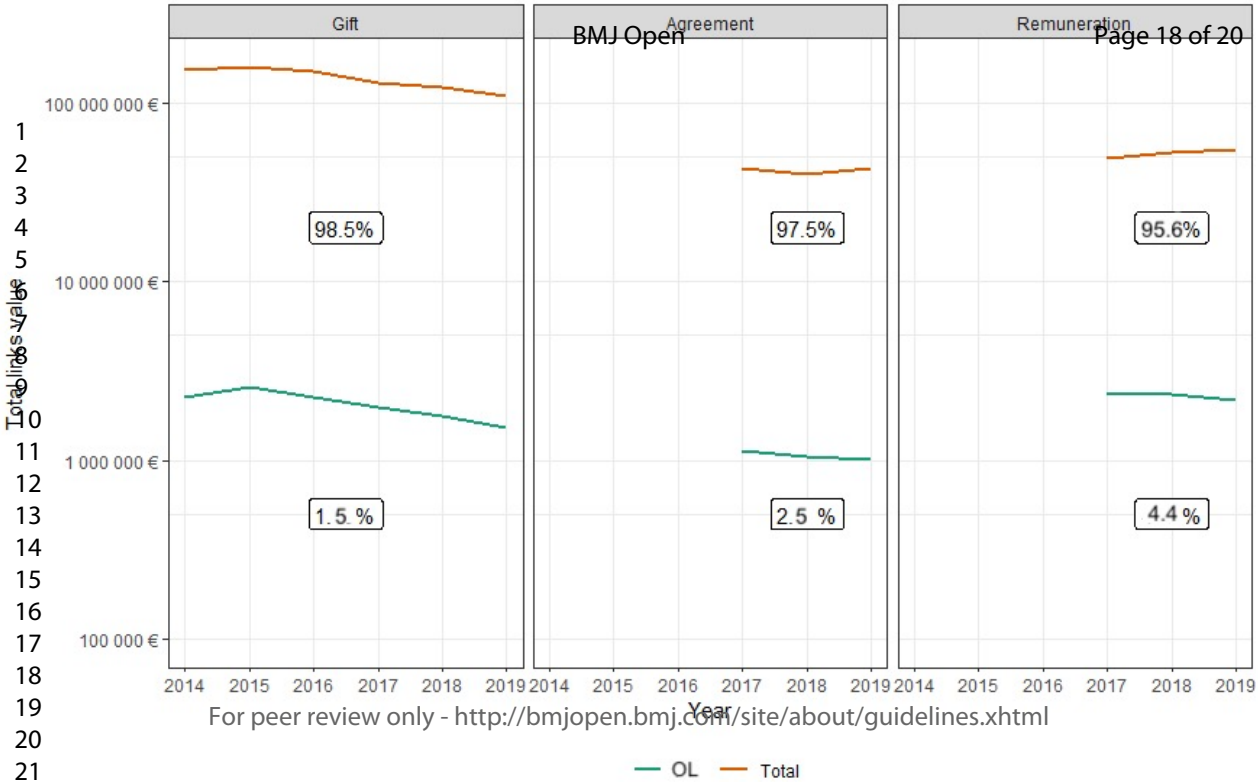
Table 2. Median (IQR) amount of gifts to KOL and non-KOL physicians in euros (€).

Gift category	*Physician category*	2014	2015	2016	2017	2018	2019
Accommodation	*All physicians*	210 (165-314)	215 (165-341)	215 (170-314)	215 (164-323)	221 (170-349)	218 (173-328)
	KOL	218 (172-305)	220 (170-330)	218 (179-296)	226 (176-313)	221 (175-323)	229 (180-344)
Hospitality	*All physicians*	50 (27-118)	45 (25-60)	46 (24-60)	55 (30-60)	53 (28-60)	52 (28-60)
	KOL	70 (30-448)	58 (28.2-258)	60 (30-258)	80.5 (40-362)	60 (29-319)	60 (30-329)
Catering	*All physicians*	40 (24-55)	40 (24-56)	38 (23-55)	38 (23-56)	38 (23-56)	38 (24-57)
	KOL	40 (23-59)	40 (23-59)	40 (23-58)	40 (23-58)	40 (24-59)	40 (24-59)
Transport	*All physicians*	208 (91-420)	200 (88-398)	191 (85-380)	189 (79-357)	182 (81-344)	177 (77-332)
	KOL	202 (70-471)	206 (74.2-461)	244 (96-477)	207 (77-445)	198 (79.8-414)	187 (71-395)
Contributions to the cost of promotional events	*All physicians*	60 (50-400)	60 (50-404)	60 (44-400)	200 (55-455)	400 (250-590)	440 (260-650)
	KOL	320 (60-591)	350 (60-600)	390 (87-650)	450 (186-729)	470 (290-740)	538 (290-796)
Donations-Grants-Training	*All physicians*	21 (17-30)	23 (17-50)	36 (23-94)	62 (30-171)	55 (29-171)	55 (25-144)
	KOL	83 (60-275)	68 (27.5-1578)	96 (63.5-138)	76 (45-192)	155 (42-225)	80 (42-180)
Service and consulting	*All physicians*	26 (22-30)	30 (22-45)	30 (24-50)	30 (25-40)	50 (25-80)	116 (40-362)
	KOL	30 (24-120)	47 (29-325)	65 (30-600)	32 (25-83)	130 (74-309)	158 (69-506)
Other	*All physicians*	100 (30-350)	140 (30-496)	100 (19-375)	22 (16-84)	25 (16-104)	49 (16-220)
	KOL	337 (34.8-1000)	800 (195-1188)	700 (100-1000)	310 (23-915)	40 (12-153)	79.5 (12-500)
TOTAL	*All physicians*	45 (25-60)	45 (25-60)	45 (25-60)	46 (25-60)	48 (25-60)	49 (26-60)
	KOL	59 (29-198)	60 (30-224)	60 (30-217)	60 (30-213)	60 (31-214)	60 (31-210)

Table 3. Number of contractual agreements with no amount, total value of agreements for which an amount could be found and number of agreements with a declared amount in the contractual agreement section, total and median (IQR) amount of remunerations to KOL and non-KOL physicians, year by year since they are consistently declared.

Payment category	Physicians category	Amount	2017	2018	2019	Total
Contractual agreements	*All physicians*	Number of agreements for which the amount could not be found in the agreement section (percentage of the number of agreements)	446,204 (79%)	443,687 (79%)	394,393 (72%)	1,284,284
		Total value of agreements for which an amount could be found in the agreement section in €	42,905,877	39,962,079	43,098,150	125,966,106
		Number of agreements with a declared amount in the agreement section	118,860	119,844	150,987	389,691
	KOL	Number of agreements for which the amount could not be found in the agreement section (percentage of the number of agreements)	3,514 (80%)	3,319 (80%)	2,663 (76%)	9,496
		Total value of agreements for which an amount could be found in the agreement section in €	1,123,947	1,040,295	1,000,651	3,164,893
		Number of agreements with a declared amount in the agreement section	903	837	843	2,583
Remunerations	*All physicians*	Total amount in €	49,152,264	53,142,546	54,254,342	156,549 152
		Median (IQR)	300 (65-750)	350 (65-800)	130 (50-613)	250
		Number of remunerations	77,277	77,436	96,160	250,573
	KOL	Total amount in €	2,355,894	2,346,293	2,172,827	6,875,014
		Median (IQR)	946 (527-1440)	1,000 (600-1497)	998 (538-1375)	1,000
		Number of remunerations	1,950	1,901	1,876	5,718





Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	#4	Present key elements of study design early in the paper	3
Setting	#5	Describe the setting, locations, and relevant dates, including periods of	3

		recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	4
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	4
Bias	#9	Describe any efforts to address potential sources of bias	4
Study size	#10	Explain how the study size was arrived at	4
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	4
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	4
Statistical methods	#12c	Explain how missing data were addressed	4
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	4
Statistical methods	#12e	Describe any sensitivity analyses	4
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	5
Participants	#13b	Give reasons for non-participation at each stage	5
Participants	#13c	Consider use of a flow diagram	5

Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	5
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	5
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	5
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
Main results	#16b	Report category boundaries when continuous variables were categorized	5
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	5
Discussion			
Key results	#18	Summarise key results with reference to study objectives	7
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	7
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	7
Generalisability	#21	Discuss the generalisability (external validity) of the study results	7
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9