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Influence of smoking on levels of urinary 8-iso Prostaglandin F2α

Angela van der Plas*, Sandrine Pouly, Guillaume de La Bourdonnaye, Gizelle Baker, Frank Lüdicke

PMI R&D, Philip Morris Products S.A., Quai Jeanrenaud 5, CH-2000, Neuchâtel, Switzerland

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ABSTRACT

Background: To evaluate the reduced-risk potential of alternative tobacco products, biomarkers that are involved in the biological pathways affected by cigarette smoking and smoking cessation are needed. Isoprostanes, a measure of oxidative stress, appear to be influenced by smoking and reversible upon smoking cessation and therefore could be a good biomarker. This review aims at quantifying the effect of smoking and smoking cessation on levels of urinary 8-iso prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$), an isoprostane.

Methods: PubMed and Scopus databases were searched for publications that reported 8-epi-$PGF_{2\alpha}$ levels in smokers and nonsmokers as well as articles reporting the effect of smoking cessation on 8-epi-$PGF_{2\alpha}$ levels.

Results: Eighteen studies assessing 8-epi-$PGF_{2\alpha}$ levels by smoking status were identified. Five of the papers reported the results as quantity excreted in 24-hour urine (μg/24 h), and 15 reported creatinine adjusted values. The meta-analyses show increased levels of 8-epi-$PGF_{2\alpha}$ in current smokers compared with nonsmokers (mean difference = 0.16, 95% confidence interval [95%CI]: 0.14–0.19 μg/24 h with inconsistency statistic [I^2] = 98%; mean difference = 172.38, 95%CI: 152.75–192.01 pg/mg creatinine with I^2 = 89%, respectively). There were too few publications to perform a meta-analysis assessing the effects of smoking cessation on 8-epi-$PGF_{2\alpha}$ levels.

Conclusions: Due to the high heterogeneity among the studies included in these meta-analyses, it is difficult to generalize the results; however, our study indicates increased levels of 8-epi-$PGF_{2\alpha}$ and therefore increased oxidative stress in smokers compared with nonsmokers. More studies are still needed to assess if 8-epi-$PGF_{2\alpha}$ levels are reversible after cessation.

1. Introduction

Cigarette smoking is one of the most important preventable risk factors for the development of atherosclerosis and cardiovascular disease (CVD) [1]. The main mechanisms through which smoking increases the risk of CVD include the alteration of lipid levels [2], inflammation, and oxidative stress, among other pathways [3]. However, the precise causative biochemical mechanisms behind the increased risk for disease in smokers are not completely understood [4], and the relationship between specific tobacco constituents and mechanistic steps involved in these diseases remains unclear [5].

Alternative products to cigarettes that can potentially reduce exposure and risk to smokers who would otherwise continue smoking are being developed and marketed. In order to assess whether the use of these products will translate into a reduction in the risk and harm caused by smoking cigarettes, the scientific community needs to identify and validate biomarkers that are predictive of a reduction in disease risk [6]. The search for biomarkers must consider molecules that are involved in biological pathways known to be affected by cigarette smoking and smoking cessation, such as those involved in the inflammatory response [7,8] and oxidative stress [3]. 8-iso prostaglandin F2α (8-epi-$PGF_{2\alpha}$)[1] is an endpoint that could potentially be used, because it is part of the family of isoprostanes. Among these, 8-epi-$PGF_{2\alpha}$ has been examined in more detail [9] and has been proven to be a potent vasoconstrictor [10], mitogen, and mild pro-aggregatory agent [11], promoting atherogenesis [9]. In arterial blood, 8-epi-$PGF_{2\alpha}$ levels increase with hyperlipidemia, cigarette smoking, and diabetes [9], and the measurement of urinary 8-epi-$PGF_{2\alpha}$ levels has been shown to be a reliable marker for in vivo oxidative stress [12,13].

Several studies have compared levels of 8-epi-$PGF_{2\alpha}$ in smokers and nonsmokers [5,14] and found that smokers tend to have higher levels of 8-epi-$PGF_{2\alpha}$, although results vary by sex [15]. This research summarizes the available literature on 8-epi-$PGF_{2\alpha}$ levels in smokers and nonsmokers as well as the influence of smoking cessation on 8-epi-$PGF_{2\alpha}$ levels.

* Corresponding author.
E-mail address: angela.vanderplas@pmi.com (A. van der Plas).

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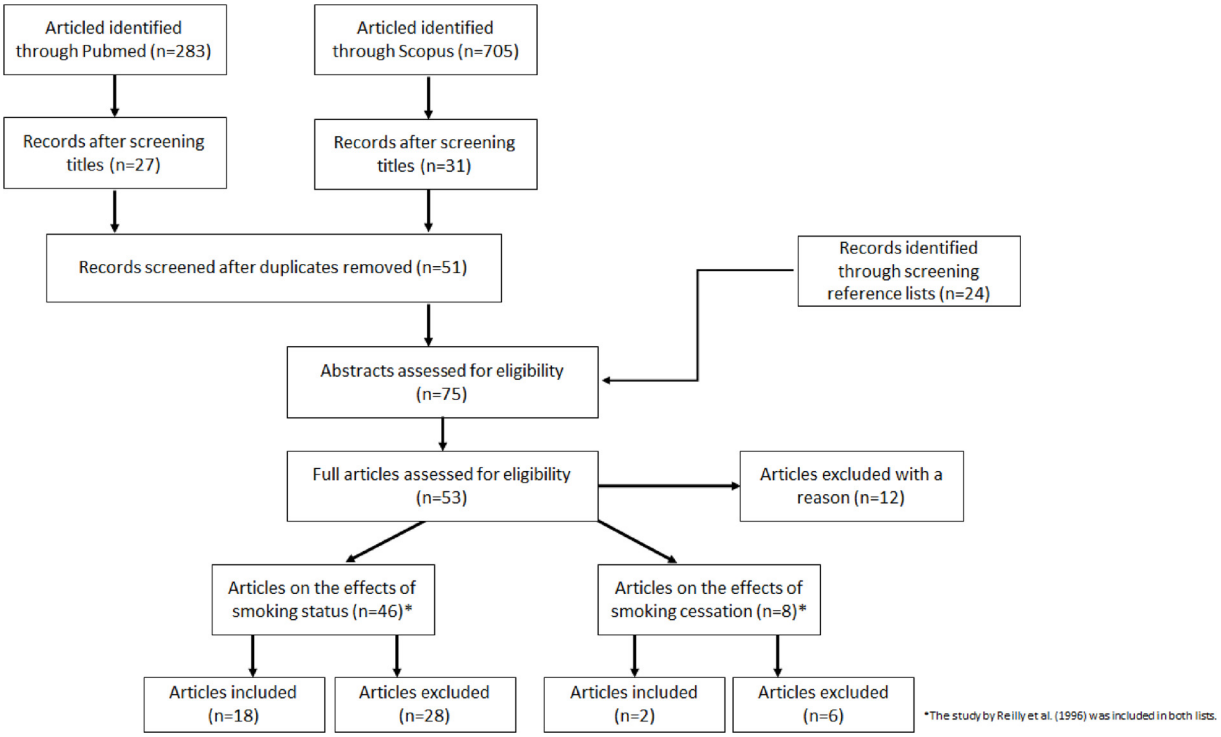

Fig. 1. Flow diagram – article retrieval process.

2. Materials and methods

2.1. Search for articles

Literature searches in Medline were performed through PubMed and Scopus to identify studies that evaluated the relationship between smoking or smoking cessation and 8-epi-$PGF_{2\alpha}$ levels. The final search was performed on March 5, 2018.

The PubMed query was: (("prostaglandins"[MeSH Terms] OR "prostaglandins"[All Fields] OR "prostaglandin"[All Fields]) AND alpha [All Fields]) AND (("tobacco"[MeSH Terms] OR "tobacco"[All Fields] OR "tobacco products"[MeSH Terms] OR ("tobacco"[All Fields] AND "products"[All Fields]) OR "tobacco products"[All Fields]) OR ("smoking"[MeSH Terms] OR "smoking"[All Fields]) OR cessation[All Fields] OR quitting[All Fields]). The query used in Scopus was: Prostaglandin alpha AND (tobacco OR smoking OR cessation OR quitting).

Retrieval of articles was limited to studies conducted in humans and written in English. To ensure that all available studies were retrieved, the reference lists of the publications obtained through the original search were reviewed to identify additional articles.

2.2. Study selection

The following criteria were used to include publications in the review:

- Case control or cohort studies (observational and experimental studies)
- Adult, healthy human populations were studied
- Measurements of 8-epi-$PGF_{2\alpha}$ by exposure group are presented as mean values by group with the standard deviation (SD) or standard error (SE) of the mean, sample size per group, or with enough information to allow for the calculation of the mean and SD

The following criteria were used to exclude publications from the review:

- Review articles, case reports, or editorials
- Results were not reported in urine
- Reports had incomplete data or included data that could not be incorporated into the review
- Articles included diseased populations
- Data were reused in a more recent study

2.3. Data extraction

Two researchers extracted the data independently; when discrepancies were identified in the data, the discrepancies were discussed, and consensus was reached for all items. The following information was extracted from each study: first author's name, year of publication, study design and population characteristics, number of participants per group, mean, SD or SE.

Not all articles reported the measurements in the same units, so values were transformed to either pg/mg of creatinine or μg/24 h. Transformations were used to convert from the median and range to the mean using the calculations postulated by Hozor et al. [16].

2.4. Statistical analysis

Pooled means were calculated for each exposure group (smokers and nonsmokers) by weighting the individual studies using their inverse pooled variance. To quantify the effects of smoking on 8-epi-$PGF_{2\alpha}$ levels, pooled mean differences between smokers and nonsmokers and 95% confidence intervals (95%CI) were calculated using the fixed effects and random effects models in Review Manager 5.3 (RevMan 5.3) (Cochrane Collaboration, Oxford, UK). These two methods are used because while a fixed effect meta-analysis assumes that all studies are estimating the same (fixed) treatment effect, a random effects meta-analysis allows for differences in the treatment effect (or exposure) from study to study (inter-study heterogeneity) (17). The degree of heterogeneity between the study results was tested by the inconsistency statistic (I^2). Funnel plots were used to evaluate publication bias [18]. Statistical significance was assessed at $\alpha = 0.05$.

Table 1
Characteristics of studies assessing levels of 8-epi-$PGF_{2\alpha}$ in smokers vs. nonsmokers.

Reference	Country	Study design	Study participants	Smoking definition	Subgroup			Units	Adjustment
					Smokers mean ± SD	Nonsmokers mean ± SD	Mean difference Δ (95%CI)		
Reilly et al. [45]	U.S.	Cross-sectional	5 heavy smokers and 14 nonsmokers. Men and women aged 20–47 years	≥30 CPD	≥30 CPD 553.10 ± 214.42	169.53 ± 31.66	383.57 (194.90, 572.24)	pg/mg creatinine	Subjects were age and sex matched
Obata et al. [46]	Japan	Cross-sectional	81 smokers aged 37.6 ± 11.1 years and 39 nonsmokers aged 38.6 ± 10.9 years	None	All 605.20 ± 59.00	424 ± 70.40	181.17 (155.62, 206.72)	pg/mg creatinine	None
Dillon et al. [47]	U.K.	Cross-sectional	10 smokers aged 41 ± 4.1 years and 10 nonsmokers aged 41 ± 4 years	None	All 1579.37 ± 266.36	852.36 ± 166.10	726.64 (532.08, 921.20)	pg/mg creatinine	None
Liang et al. [48]	U.S.	Cross-sectional	41 men and women aged 32–80 years	None	Men 500 ± 370 Women 620 ± 430	160 ± 70 330 ± 160	340 (148.24, 531.76) 290 (–141.87, 721.87)	pg/mg creatinine	None
Jacob et al. [49]	U.S.	Cross-sectional	77 healthy men aged 35.6 ± 9.2 years for smokers and 34 ± 7.6 years for nonsmokers	None	All 830 ± 930	730 ± 660	100.00 (–261.03, 461.03)	pg/mg creatinine	None
Harman et al. [50]	U.S.	Cross-sectional	80 smokers and 96 nonsmokers aged 19–80 years	≥ 10 CPD	All 1100 ± 894.43	510 ± 391.92	590 (378.90, 801.10)	pg/mg creatinine	None
Zedler et al. [51]	U.S.	Cross-sectional	36 smokers aged 35.8 ± 11.1 years and 65 nonsmokers aged 36 ± 13.6 years	None	Men 2140.75 ± 980.25 Women 2230.50 ± 749.50	1183.75 ± 398.75 1170.00 ± 264.50	957.00 (482.21, 1431.72) 1060.50 (703.34, 1417.66)	pg/mg creatinine	None
Yan et al. [52]	U.S.	Interventional	32 smokers aged 44 ± 9 years and 12 nonsmokers aged 44 ± 7 years	None	Men 853 ± 545 Women 1259 ± 516 Men 1.30 ± 0.66 Women 1.18 ± 0.47	768 ± 175 1204 ± 473 1.42 ± 0.38 1.26 ± 0.46	85.00 (–216.53, 386.53) 55.00 (–400.16, 510.16) –0.12 (–0.56, 0.33) –0.08 (–0.51, 0.36)	pg/mg creatinine μg/24 hours	Yes, but variables were not mentioned
Taylor et al. [53]	U.S.	Cross-sectional	25 participants men and women aged 18–35 years	10–20 CPD	Men 430.00 ± 146.97 Women 520.00 ± 84.84	280.00 ± 24.49 430.00 ± 134.16	150.00 (30.78, 269.22) 90.00 (–49.31, 229.31)	pg/mg creatinine	None
Takeshita et al. [54]	Japan	Cohort	11 smokers aged 24.2 ± 2.2 years and 11 nonsmokers aged 24.9 ± 3.6 years	None	All 231.90 ± 63.2	All 173.80 ± 39.80	All 58.10 (13.96, 102.24)	pg/mg creatinine	None
Basu et al. [15]	Sweden, Italy, and Poland	Cross-sectional	217 smokers and 89 nonsmokers aged 17–66 years	None	Men 918.95 ± 475.53 Women 1063.90 ± 498.25	1302.85 ± 1140.36 724.67 ± 292.48	–383.90 (–564.96, –202.84) 339.23 (223.22, 455.24)	pg/mg creatinine	None
Sakano et al. [55]	Japan	Cross-sectional	323 subjects aged 20–65 years	None	All 900.00 ± 393.95	680.00 ± 450.99	220.0 (122.00, 318.00)	pg/mg creatinine	None
Calapai et al. [56]	Italy	Cross-sectional	20 smokers and 20 never-smokers aged 23–73 years	None	All 933.00 ± 402.10	781.00 ± 329.50	152.00 (–79.39, 383.39)	pg/mg creatinine	None
Lowe et al. [5]	U.K.	Cross-sectional	80 men and women aged 21 years and above	≥20 CPD	All 1.48 ± 0.72 All 1035.40 ± 361.40	0.92 ± 0.64 611.50 ± 211.20	0.56 (0.13, 0.99) 423.90 (239.22, 608.58)	μg/24 hrs pg/mg creatinine	None
Andreoli et al. [57]	Italy	Cross-sectional	22 twin pairs, men and women aged 23–46 years	Tar intake (ISO) ≥60 mg a day	All 1.25 ± 0.60	0.92 ± 0.43	0.33 (0.02, 0.64)	μg/24 hrs	None
Frost Pineda et al. [58]	U.S.	Cross-sectional	3322 smokers aged 43.3 ± 14.7 years and 1044 nonsmokers aged 41.7 ± 12.71 years	None	All 1.89 ± 1.05	1.33 ± 0.75	0.56 (0.50, 0.62)	μg/24 hrs	None

(*continued on next page*)

Table 1 (*continued*)

Reference	Country	Study design	Study participants	Smoking definition	Subgroup			Units	Adjustment
					Smokers mean ± SD	Nonsmokers mean ± SD	Mean difference Δ (95%CI)		
Campos et al. [59]	Spain	Cross-sectional	22 smokers aged 37 ± 14 and 38 nonsmokers aged 38.7 ± 14.8 years	Mean 12 CPD	All 1,410 ± 820	1,010 ± 400	400.00 (34.51, 765.49)	pg/mg creatinine	None
Haswell et al. [14]	Germany	Cross-sectional	204 men and women aged 28–55 years	10–30 CPD	All 0.25 ± 0.12	0.17 ± 0.06	0.08 (0.05, 0.11)	µg/24 hrs	None

CPD: cigarettes per day.

3. Results

A flow diagram detailing the retrieval process of articles from the different sources used can be found in Fig. 1. There were 238 publications retrieved from the PubMed search and 705 retrieved from the Scopus search. Of these, 51 articles remained after screening for duplicates and review of the titles among the search results. The reference lists of these articles were reviewed, and 24 additional records were identified. In total, 75 abstracts were reviewed, and 54 articles remained for full review. For the analysis of smoking status and its association to 8-epi-$PGF_{2\alpha}$ levels, a total of 46 publications that assessed the effect of smoking status were identified. Out of the 46 publications, 18 articles were included in the analyses.

Table 1 presents the characteristics for the 18 publications that were included in the analyses. The reasons for exclusion of 28 articles were that one evaluated the acute effects of smoking [19], one reported levels in bronchoalveolar lavage [20], two reported levels in exhaled breath condensate [21,22], one reported levels in lymphatic vessels [23], three reported plasma levels [24–26], one reported saliva levels [27], two reported levels in sputum [28,29], four reported data from diseased populations [30–33], eight had incomplete information [4,34–40], one presented log-transformed values [41], and four others reported units that could not be used [12,42–44]. A list of the 75 publications from which abstracts were screened can be found in Supplement 1. For the analysis to assess the effect of smoking cessation on 8-epi-$PGF_{2\alpha}$ levels, eight studies were identified, but only two had complete data that could potentially be used in a meta-analysis [45,60]. No meta-analysis was performed due to either incomplete information or lack of enough studies with the same follow-up time. Study characteristics can be found in Table 2.

3.1. Effects of smoking status on 8-epi-$PGF_{2\alpha}$ levels

Due to studies reporting different measurement units, there were two meta-analyses performed. The first meta-analysis used concentrations adjusted for creatinine concentration (pg/mg creatinine), and the second used daily excretion (µg/24-hour urine). The results of the meta-analyses can be found in Table 2. The meta-analysis included 15 studies reporting 18 comparisons [5,15,45–56,59]. The pooled analysis showed increased levels of 8-epi-$PGF_{2\alpha}$ in smokers compared with nonsmokers (mean difference: 172.38, 95%CI: 152.75, 192.01 pg/mg creatinine), and it showed significant heterogeneity (I^2: 89%, $p < 0.001$). The Forest plot for this meta-analysis can be found in Fig. 2. The random effect analysis confirmed the results (mean difference: 274.51, 95%CI: 186.16, 359.86 pg/mg creatinine). The Forest plot for this meta-analysis can be found in Fig. 3. The meta-analysis looking at daily excretion of 8-epi-$PGF_{2\alpha}$ included five studies with six comparisons [5,14,52,57,58], with the pooled mean difference showing increased levels in smokers compared with nonsmokers (mean difference: 0.16, 95%CI: 0.14, 0.19 µg/24 h). The Forest plot for this meta-analysis can be found in Fig. 4. The heterogeneity in this analysis was also significant (I^2: 98%, $p < 0.001$). The random effect analysis rendered the results not statistically significant (mean difference: 0.24, 95%CI: –0.05, 0.53 µg/24 h). The Forest plot for this meta-analysis can be found in Fig. 5. After inspection of the funnel plots (Figs. 6 and 7), there

Table 2
Meta-analysis results on smoking and 8-epi-$PGF_{2\alpha}$ levels.

Meta-analyses	Studies (estimates)	Mean difference (95%CI)		
		Fixed effects	I^2 (%)	Random effects
µg/24 h	5 (6)	0.16 (0.14, 0.19)	98	0.24 (–0.05, 0.53)
pg/mg creatinine	15 (18)	172.38 (152.75, 192.01)	89	274.51 (189.16, 359.86)

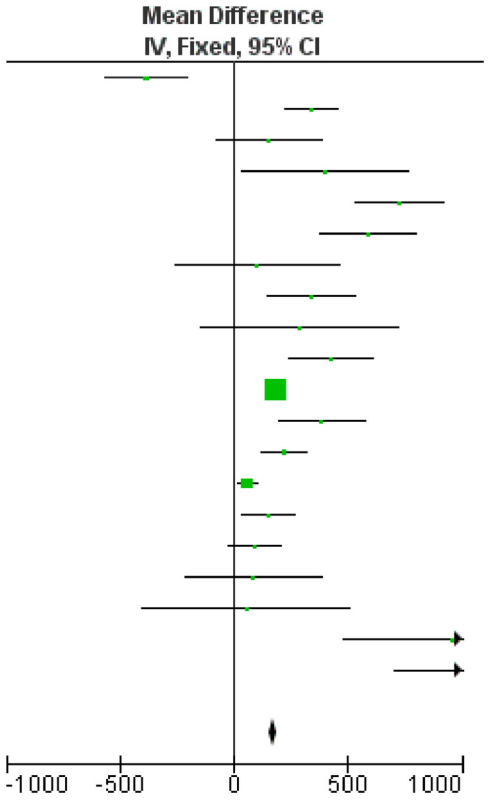

Fig. 2. Forest plot for the fixed effects meta-analysis of 8-epi-$PGF_{2\alpha}$ (pg/mg creatinine) levels in smokers vs. non-smoker.

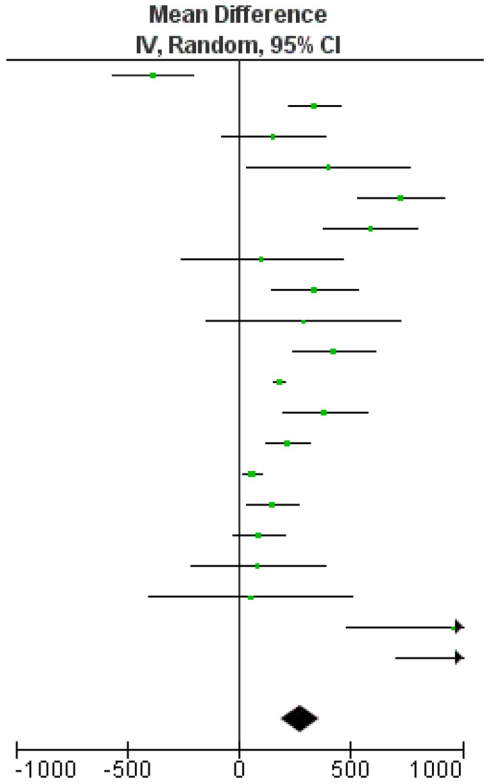

Fig. 3. Forest plot for the random effects meta-analysis of 8-epi-$PGF_{2\alpha}$ (pg/mg creatinine levels in smokers vs. non-smokers.

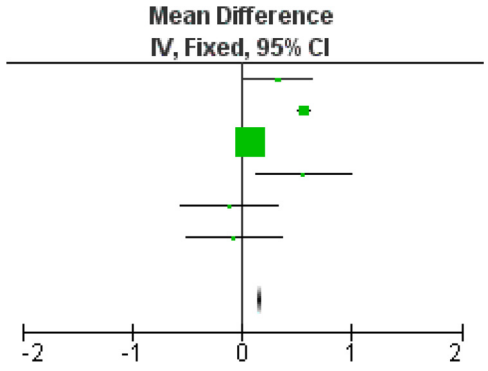

Fig. 4. Forest plot for the fixed effects meta-analysis of 8-epi-$PGF_{2\alpha}$ (μg/24 h) levels in smokers vs. non-smokers.

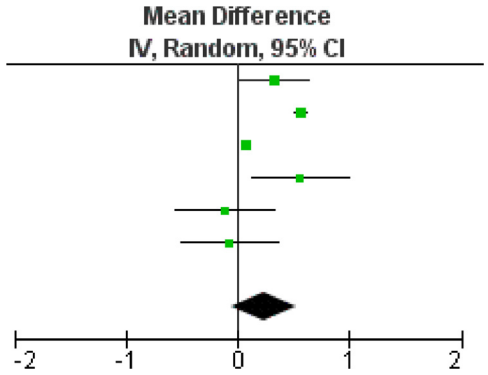

Fig. 5. Forest plot for the random effects meta-analysis of 8-epi-$PGF_{2\alpha}$ (μg/24 h) levels in smokers vs. non-smokers.

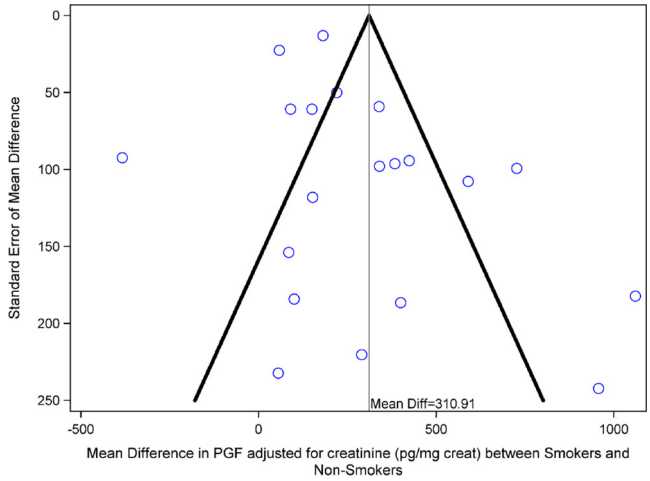

Fig. 6. Funnel plot of studies reporting 8-epi-$PGF_{2\alpha}$ levels in pg/mg creatinine.

was no evidence of publication bias in the meta-analyses.

3.2. Effects of smoking cessation on 8-epi-$PGF_{2\alpha}$ levels

The searches in PubMed and Scopus and the review of the reference lists yielded eight studies assessing the influence of smoking cessation on 8-epi-$PGF_{2\alpha}$ levels. Out of these eight studies, only two reported complete information. Therefore, no meta-analysis could be performed [45,60]. The results of these studies can be found in Table 3. The rest of the studies were performed in diseased populations [30,61], did not provide complete information [42,62,63], or compared differences between smokers and ex-smokers with unknown follow-up time [64].

Of the two studies reporting results, the study by Reilly et al. [45]

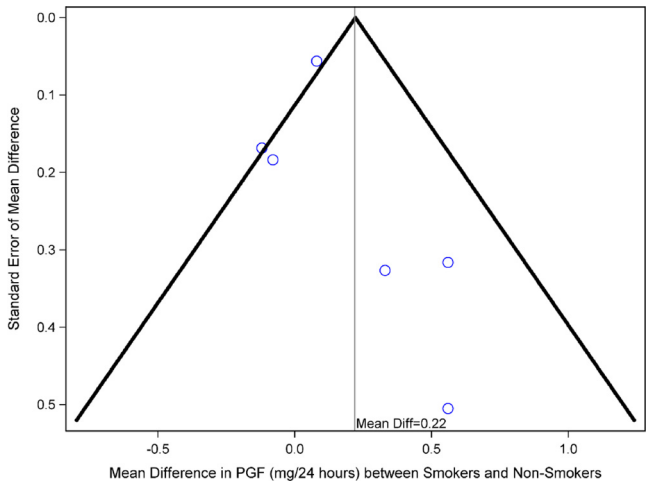

Fig. 7. Funnel plot of studies reporting 8-epi-$PGF_{2\alpha}$ levels in μg/24 h.

reports decreasing levels of 8-epi-$PGF_{2\alpha}$ after two to three weeks of smoking cessation, whereas the study by Lüdicke et al. [60] reports that there was an increase in 8-epi-$PGF_{2\alpha}$ levels 90 days after cessation.

4. Discussion and conclusions

The present study summarizes the evidence that smokers have higher 8-epi-$PGF_{2\alpha}$ levels compared with non-smokers via two meta-analyses, which had not been done previously. We performed meta-analyses of published articles on the association of smoking and 8-epi-$PGF_{2\alpha}$ levels. The retrieved studies presented data in different units; therefore, two meta-analyses were performed. The relationship of smoking cessation to 8-epi-$PGF_{2\alpha}$ levels could not be evaluated through meta-analyses, as not enough articles with complete information were identified. The results of the smoker to nonsmoker comparisons show that smokers had statistically significant higher levels of 8-epi-$PGF_{2\alpha}$. There was, however, very high inter-study heterogeneity, and after running random effect model meta-analyses, one of the results was no longer statistically significant. Because the random effects model takes into account the variability of the exposure effect, analyses under this model result in an estimate of the average effect rather than the common effect of smoking on 8-epi-$PGF_{2\alpha}$ levels [17]. Performing sensitivity analysis (looking into the heterogeneity that single studies contribute to the meta-analysis) in the pg/mg creatinine analysis, the studies by Basu et al. [15], Harman et al. [50], Takeshita et al. [54], Lowe et al. [5], Dillon et al. [47], and Zedler et al. [51] accounted for most of the heterogeneity, and excluding these studies lowered the inter-study heterogeneity significantly without changing the results of the meta-analysis (mean difference: 183.72, 95%CI: 160.70, 206.74, $p < 0.001$, I^2: 13%). Limiting the number of studies to Asian or Western countries did not decrease the heterogeneity I^2 value. Finally, in the meta-analysis using μg/24 h values, the studies by Frost Pineda et al. [65] and Lowe et al. [5] accounted for most of the inter-study heterogeneity, most likely because the reported values corresponded to the two highest [5,65] from the studies. Excluding these studies did not change the results of the meta-analysis (mean difference: 0.08, 95%CI: 0.05, 0.11, $p < 0.001$, I^2: 21% versus 0.16, 95%CI: 0.14-0.19, I^2: 98%), and the heterogeneity was no longer significant.

Despite the high heterogeneity found in the meta-analyses, these showed increased levels of 8-epi-$PGF_{2\alpha}$ in smokers compared with nonsmokers. On the other hand, 8-epi-$PGF_{2\alpha}$ levels do not seem to be affected by smoking cessation, as out of the two studies with complete data retrieved, one showed decreased levels after two to three weeks of quitting [45], while the second reported higher levels of 8-epi-$PGF_{2\alpha}$ 90 days after cessation [60].

Cigarette smoking is a strong risk factor for pulmonary disease as

Table 3
Characteristics of studies assessing the influence of cessation on levels of 8-epi-$PGF_{2\alpha}$.

Study	Country	Study design	Study participants	Treatment	Findings
Reilly et al. [45]	U.S.	Interventional	6 male chronic smokers aged 20–47 years and smoking 15–45 CPD	Volunteers were given nicotine patches	Levels of 8-epi-$PGF_{2\alpha}$ fell from 145.5 ± 24.9 (mean SEM) to 114.6 ± 27.1 ($p < 0.05$) pmol/mmol creatinine two weeks after cessation and 112.6 ± 24.9 three weeks after cessation ($p < 0.05$)
Lüdicke et al. [60]	Japan	Interventional	166 male and female smokers aged 23–65 years who reported having smoked ≥10 CPD and ≥3 years were randomized to a heat-not-burn product, smoking abstinence, or continued smoking	Participants in the smoking abstinence arm were given psychological support	Levels of 8-epi-$PGF_{2\alpha}$ increased from 198.47 pg/mg creatinine (95%CI: 176.89, 222.68) at baseline to 206.59 pg/mg creatinine (95%CI: 178.59, 238.98) 90 days after cessation

CPD: cigarettes per day.

well as CVD [66]. Smoking cessation is the recommended method of avoiding such increased risk [5], but cessation is also difficult to achieve [67]. Because of these facts, the U.S. Food and Drug Administration published draft guidelines for the tobacco industry for the marketing authorization of tobacco products that would decrease the exposure to tobacco toxicants and/or reduce the risk to tobacco-associated diseases [68]. One of the ways to approach the evaluation of risk reduction is through the usage of clinical risk endpoints [5]. Such endpoints should, in principle, be associated with smoking as well as influenced by smoking cessation, such as 8-epi-$PGF_{2\alpha}$.

These meta-analyses showed that 8-epi-$PGF_{2\alpha}$ levels are elevated in smokers versus nonsmokers, while more studies assessing the changes in 8-epi-$PGF_{2\alpha}$ after smoking cessation are needed to evaluate the reversibility of this marker as a clinical risk endpoint.

Conflict of interest

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Transparency document

The Transparency document associated with this article can be found in the online version.

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