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Research Paper

Strategies to decrease oxidative stress biomarker levels in human medical conditions: A meta-analysis on 8-iso-prostaglandin $F_{2\alpha}$

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A B S T R A C T

The widespread detection of elevated oxidative stress levels in many medical conditions has led to numerous efforts to design interventions to reduce its effects. Efforts have been wide-ranging, from dietary changes to administration of antioxidants, supplements, *e.g.,* omega-3-fatty acids, and many medications. However, there is still no systemic assessment of the efficacy of treatments for oxidative stress reduction across a variety of medical conditions.

The goal of this meta-analysis is, by combining multiple studies, to quantitate the change in the levels of the popular oxidative stress biomarker 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) after a variety of treatment strategies in human populations.

Nearly 350 unique publications with 180 distinct strategies were included in the analysis. For each strategy, the difference between pre- or placebo and post-treatment levels calculated using Hedges' g value of effect. In general, administration of antibiotics, antihyperlipidemic agents, or changes in lifestyle ($g = -0.63, -0.54$, and 0.56) had the largest effect. Administration of supplements, antioxidants, or changes in diet ($g = -0.09, -0.28, -0.12$) had small quantitative effects. To fully interpret the effectiveness of these treatments, comparisons to the increase in g value for each medical condition is required. For example, antioxidants in populations with coronary artery disease (CAD) reduce the 8-iso-$PGF_{2\alpha}$ levels by $g = -0.34 \pm 0.1$, which is quantitatively considered a small effect. However, CAD populations, in comparison to healthy populations, have an increase in 8-iso-$PGF_{2\alpha}$ levels by $g = 0.38 \pm 0.04$; therefore, the overall reduction of 8-iso-$PGF_{2\alpha}$ levels is $\approx$ 90% by this treatment in this specific medical condition.

In conclusion, 8-iso-$PGF_{2\alpha}$ levels can be reduced not only by antioxidants but by many other strategies. Not all strategies are equally effective at reducing 8-iso-$PGF_{2\alpha}$ levels. In addition, the effectiveness of any strategy can be assessed only in relation to the medical condition investigated.

1. Introduction

With the increasing acceptance of oxidative stress as a potential deleterious mechanism to human health, much research now focuses on strategies to reduce oxidative stress with the goal of improving health. Many different approaches have been investigated with the most common strategy involving elevating the total level of antioxidants [1–16]. This is typically accomplished through supplementation with high levels of classic antioxidants, e.g., vitamin C, E, or glutathione [17], or engineered nutraceutical blends high in a mixture of these and other compounds [18]. In addition, changes in diet or consumption of extracts [19] are commonly used to modify antioxidants levels. Another common approach to reducing bodily oxidative stress is to modify the rate of oxidant production. Typical strategies in this category are lifestyle changes or treatment of underlying diseases by medications [20]. It is also believed that some medications can be antioxidants.

With this large variety of potential approaches, determining the most effective method becomes crucial. Here we systemically review and quantitatively compare a wide variety of strategies that have been shown to reduce biomarkers of oxidative stress in humans. There are numerous biomarkers that could be utilized to quantitate the levels of oxidative stress. Through the multi-model, multi-laboratory Biomarkers of Oxidative Stress study, many biomarkers were compared, with the most indicative marker being the F_2-isoprostanes and specifically 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) [21–25]. Since no other biomarker is recommended, this meta-analysis will focus solely on 8-iso-$PGF_{2\alpha}$ as the biomarker. Interestingly, in addition to being a marker of oxidative stress, it is now becoming accepted that this popular biomarker can also

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be indicative of increases in inflammation, specifically through the direct generation of 8-iso-$PGF_{2\alpha}$ by prostaglandin-H-synthases (PGHS) *in vivo*. This often-overlooked, potentially confounding generation mechanism makes interpretations of elevated levels of 8-iso-$PGF_{2\alpha}$ complicated. Given this caveat, the effectiveness of strategies to reduce 8-iso-$PGF_{2\alpha}$, especially anti-inflammatory medication, should provide interesting insights into the contribution of these two sources in a wide variety of medical conditions known to have elevated 8-iso-$PGF_{2\alpha}$ levels.

This comparison of strategies for reducing 8-iso-$PGF_{2\alpha}$ provides an unbiased review of the literature without preconceived notions of the origins or mechanisms of 8-iso-$PGF_{2\alpha}$ generation. In addition, the quantitative magnitude of diminished 8-iso-$PGF_{2\alpha}$ levels for each strategy could provide clues to the role of oxidative stress in each medical condition, guiding future work to rectify past interpretations of this biomarker.

2. Materials and methods

2.1. Data collection and inclusion criteria

An electronic search for the term "isoprostanes" was performed in the Thomas Reuters Web of Knowledge database and all references imported into Endnote. This initial search was then refined by searching in the abstracts or titles specifically for the F_2-isoprostanes and, more specifically, 8-iso-$PGF_{2\alpha}$. Results from multiple acronyms and abbreviations were combined as multiple names and abbreviations are common for these biomarkers, especially in earlier publications. The following terms were included: F_2-isoprostane, 8-isoprostane, 8-iso-$PGF_{2\alpha}$, 8-epi-$PGF_{2\alpha}$, 15-F_2t-isoprostane, iPF2α-III, and isoprostane. Subsequently, references referring to animal experiments were excluded by searching for key words in the title and abstract, *e.g.,* "rat", "mouse", "mice", "pig", etc. The remaining references were manually selected for inclusion into the meta-analysis if the measurements were performed on human specimens in either randomized control trials or cross-sectional studies. In addition, sufficient data on the mean population concentration and distribution of free or total 8-iso-$PGF_{2\alpha}$ had to be reported for studies to be included. Numeric data were gathered directly from tables or, when presented in graphs, were inferred by digitizing the figure with Plot Digitizer for Windows by Joseph A. Huwaldt.[1] Numeric data collected included mean, geometric mean, standard deviation (SD), standard error (SE), interquartile range (IQR), 95% confidence interval, and number of participants (n). Geometric means and arithmetic means were used without modification. The measures of variation in the mean were converted to standard deviation prior to calculation of Hedges' g. Standard error was assumed to be SD $= SE * \sqrt{n}$. The interquartile range was assumed to be SD = IQR/1.35. The 95% confidence interval was assumed to be SD $= \sqrt{}$n*(upper limit-lower limit)/ t value. Except for serum, all biological specimens were included in the analysis. Serum is not an appropriate specimen for F_2-isoprostane measurement because, during the clotting process, 8-iso-$PGF_{2\alpha}$ is generated *ex vivo* by prostaglandin endoperoxide synthase [26]. Publications reporting storage conditions other than liquid nitrogen or − 80 °C, and the use of non-pristine samples (repeated freeze/thaw cycles) were excluded. No restrictions were placed on measurement methodology. Additional publications were found through the reference sections of already included publications. Review articles and strategies for which fewer than 3 unique publications could be found were also excluded from the final analysis. References from van 't Erve et al. [27] were used to calculate the g values for the medical condition baselines (populations with the medical conditions compared to a population without any medical conditions).

[1] http://plotdigitizer.sourceforge.net.

2.2. Meta-analysis and sensitivity analyses

Extracted mean or geometric mean, standard deviation or geometric standard deviation, and number of participants were used to compute the standardized mean difference (Hedges' g) and 95% confidence intervals using R version 3.4.0, and RStudio version 1.1.383, with the software package "meta" [28,29]. Studies reporting different grades or severities of conditions were combined to form a single estimate per the method of Borenstein et al. [30]. The fixed-effects model was used for the meta-analysis and applied to each subgroup (*i.e.*, strategy per medical condition) with inverse variance weighting of individual studies [31,32].

When studies are combined, significant heterogeneity between studies can exist and confound the analysis if not accounted for. Sensitivity analyses were performed to assess heterogeneity when studies were combined with different specimens (*i.e.*, plasma, urine, *etc.*), methodologies (*i.e.*, ELISA, mass spectroscopy, *etc.*), duration of study, and medical conditions (*i.e.*, diabetes, cardiovascular disease, *etc.*). The influence of each factor was assessed by calculating a random-effects model for all data and subsequently calculating a random-effects model of datasets filtered on each potential source of heterogeneity. These different models were compared amongst each other using the Kruskal-Wallis Rank Sum Test to see if any one model provided a statistically significantly different answer from all others with $p < 0.05$. If no statistically significant difference was observed, the parameter investigated could be combined in fixed-effect models without introducing significant bias into the final analysis.

2.3. Percent inhibition and error calculation

Effectiveness was assed as the difference between the fixed-effect model Hedges' g calculated for each strategy per medical condition (*Strategy g*) and the Hedges' g value calculated for elevated 8-iso-$PGF_{2\alpha}$ levels between populations with and without the condition (*Baseline g*), as previously calculated by van 't Erve et al. [27]. The baseline values from the earlier meta-analysis [27] were taken as 0% inhibition for each medical condition. The effect of each strategy was calculated and converted to a percentage with **Formula** (1):

$$\left[100 - \left(\frac{\text{Baseline g-(Strategy g} \times -1)}{\text{Baseline g}}\right)\right] \times 100 \quad (1)$$

The error was calculated by adding the coefficient of variation of the baseline Hedges' g to that of the Hedges' g for the strategy and multiplying this value by the percent inhibition. The error is always presented as a positive number to improve interpretation of the data. A minimum of two publications per medical condition was required for inclusion in the final analysis.

3. Results

The literature search strategy resulted in a total of 2730 unique publications on F_2-isoprostanes in humans. After removing reviews, publications with other F_2-isoprostanes (*i.e.* 8,12-iso-iPF2 alpha-VI, $IPF_{2\alpha}$-I, *etc.*), F_2-isoprostane metabolites, surgeries, publications with serum as the specimens, and publications with animals or cells, 669 publications reported on 8-iso-$PGF_{2\alpha}$ levels in appropriate human specimens and medical conditions. Of these publications, 391 included strategies to reduce 8-iso-$PGF_{2\alpha}$ (Fig. 1). 8-iso-$PGF_{2\alpha}$ was measured in almost 20,000 control samples and just over 15,000 treatment samples, resulting in 417 treatment-control pairs for which the Hedges' g values could be calculated (data points).

These data points describe the effect of 180 different strategies on the levels of 8-iso-$PGF_{2\alpha}$ in human specimens. Strategies were subjectively classified into 19 categories: anti-inflammatories, antibiotics, anticoagulants, anticonvulsants, antihyperglycemics,

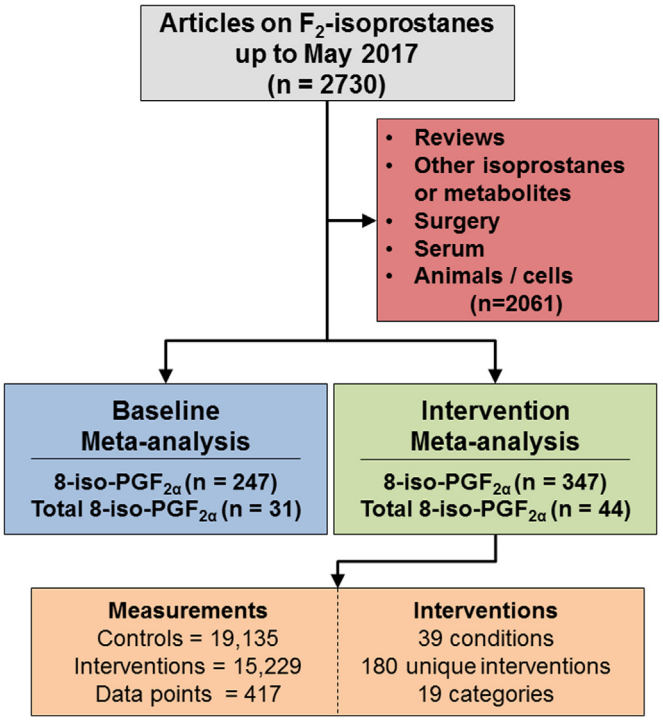

Fig. 1. Diagram of the inclusion process for the meta-analysis. N in parentheses represents the number of publications in each step, whereas the end totals represent the sum of all individuals measured for free or total 8-iso-$PGF_{2\alpha}$.

antihyperlipidemics, antihyperphosphatemias, antihypertensives, antimucolytics, antiobesities, antioxidants, antivirals, bronchodilators, diets, extracts/oils/juices, hormones, lifestyle, medical procedures/devices, phytochemicals, supplements, and uricosurics. Supplemental Table S1 lists all strategies making up each category. Diet changes were considered to be all those strategies which included addition of whole foods or changes in overall caloric content or lipid content of the diet. Extracts/oils/juices were those strategies with a processed product, *e.g.*, fish oil or green tea extract, *etc.*, but not a pure compound. Strategies concerning administration of pure chemical compounds were classified as either phytochemicals or supplements. Lifestyle changes were those strategies that relied on physical changes rather than pharmacological agents, such as smoking cessation, increased exercise, or weight loss.

To reduce the diversity between studies, the data needed to be combined in an appropriate manner. To ensure combining this many studies did not confound the analysis by introducing significant heterogeneity, sensitivity analyses were performed. The sensitivity analysis showed that Hedges' g values did not change significantly between studies with different specimens, methodologies for measuring 8-iso-$PGF_{2\alpha}$ and treatment durations for a given medical condition/strategy combination, Supplementary Fig. 1.

The remaining 278 references could be utilized to establish the increase in 8-iso-$PGF_{2\alpha}$ levels associated with medical conditions [61-351]. These increases were reported in a prior work by van 't Erve et al. [27] and are referred to as the baseline meta-analysis in this publication. The extracted data from each publication can be found in the following Mendeley dataset: ⟨http://dx.doi.org/10.17632/6s8k723m7b.1⟩.

3.1. Free 8-iso-$PGF_{2\alpha}$

In publications where no specific medical condition is reported in the studied populations (*e.g.,* having no diagnosis of a given disease or no increased risk for adverse health outcomes due to risk factors such as tobacco smoking), use of hormones ($g = -0.5 \pm 0.1$) followed by dietary ($g = -0.33 \pm 0.03$) and lifestyle changes ($g = -0.25 \pm 0.1$) show the largest reductions in 8-iso-$PGF_{2\alpha}$ levels (Fig. 2 **upper panel**). All these strategies result in a statistically significant reduction in the level of 8-iso-$PGF_{2\alpha}$; however, quantitatively, the effects are considered small (Hedges' $g < 0.7$). Additionally, administration of phytochemicals or extracts/oils/juices provided even smaller yet still statistically significant reductions in 8-iso-$PGF_{2\alpha}$. For all other strategies investigated in healthy populations, no statistically significant reduction in the level of 8-iso-$PGF_{2\alpha}$ was observed. The effects of medications are largely missing in populations without a medical condition, as these studies are not typically performed or reported on.

The strategies with the largest reduction in 8-iso-$PGF_{2\alpha}$ level in populations affected by a medical condition (*e.g.,* those *populations* having a diagnosis of a given disease or that are at increased risk for adverse health outcomes due to risk factors such as tobacco smoking), were administration of antibiotics, antihyperlipidemics, and changes in lifestyle (Fig. 2 **lower panel**). All these strategies have a statistically significantly different from 0 change in the Hedges' g value, yet quantitatively they are considered small effects (Hedges' $g < 0.7$). Interestingly, in populations administered anticonvulsants there was a large and statistically significant increase in the levels of 8-iso-$PGF_{2\alpha}$.

When comparing Hedges' g values between publications with and without a medical condition, all strategies, except dietary changes, produced a larger reduction in 8-iso-$PGF_{2\alpha}$ levels in populations with medical conditions. This is a generalized result, and since the populations with medical conditions comprised 38 different conditions, it was important to determine whether significant heterogeneity was induced when all conditions were combined. A sensitivity analysis showed that significant heterogeneity is present between the various included conditions; therefore, each strategy must be described in the context of each specific condition (Supplemental Fig. 2). In addition, as previously reported [33], the extent of reduction in the 8-iso-$PGF_{2\alpha}$ levels has been found to be proportional to the elevated levels found in each medical condition relative to the level of a healthy population. Therefore, results are presented as percent inhibition for each strategy per medical condition (Fig. 3). The analysis was restricted to those medical conditions where a Hedges' g for the baseline elevation of 8-iso-$PGF_{2\alpha}$ was available as well as those strategies which had at least two publications per category to calculate the Hedges' g value.

Percent inhibition within each category varied significantly between medical conditions. In general, the largest inhibitions were observed with lifestyle changes and extracts/oils/juices (Fig. 3). Weight loss in obese populations led to the largest percentage reduction in 8-iso-$PGF_{2\alpha}$ levels of all strategies studied. Also, a large percentage reduction was observed in tobacco smokers from an extract, oils, or a juice; however, this group consists of only two references and therefore has a large uncertainty. The category with the most consistent and statistically significant reduction in percentage of 8-iso-$PGF_{2\alpha}$ compared to baseline was the antioxidants. Populations with medical conditions that did not see a significant reduction in 8-iso-$PGF_{2\alpha}$ after antioxidant supplementation were chronic kidney disease, cystic fibrosis, and obesity. Antioxidant supplementation in tobacco smokers had a small but statistically significant reduction in 8-iso-$PGF_{2\alpha}$ inhibition percentage. For treatments with medications, statistically significant decreases in 8-iso-$PGF_{2\alpha}$ levels were observed with both antihyperlipidemic and antihypertensive drugs in populations diagnosed with hyperlipidemia. In addition, statistically significant reductions were found in populations with hypertension being treated with antihypertensive drugs. Anti-inflammatories, dietary changes, and supplements had mostly non-significant and very small effects; a notable exception to this is that dietary changes in populations with hypertension had a large and significant effect, an effect driven predominantly by the effectiveness of the "dietary approach to stop hypertension" (DASH) diet. See the Supplemental forest plots for a detailed presentation of the data in Fig. 3.

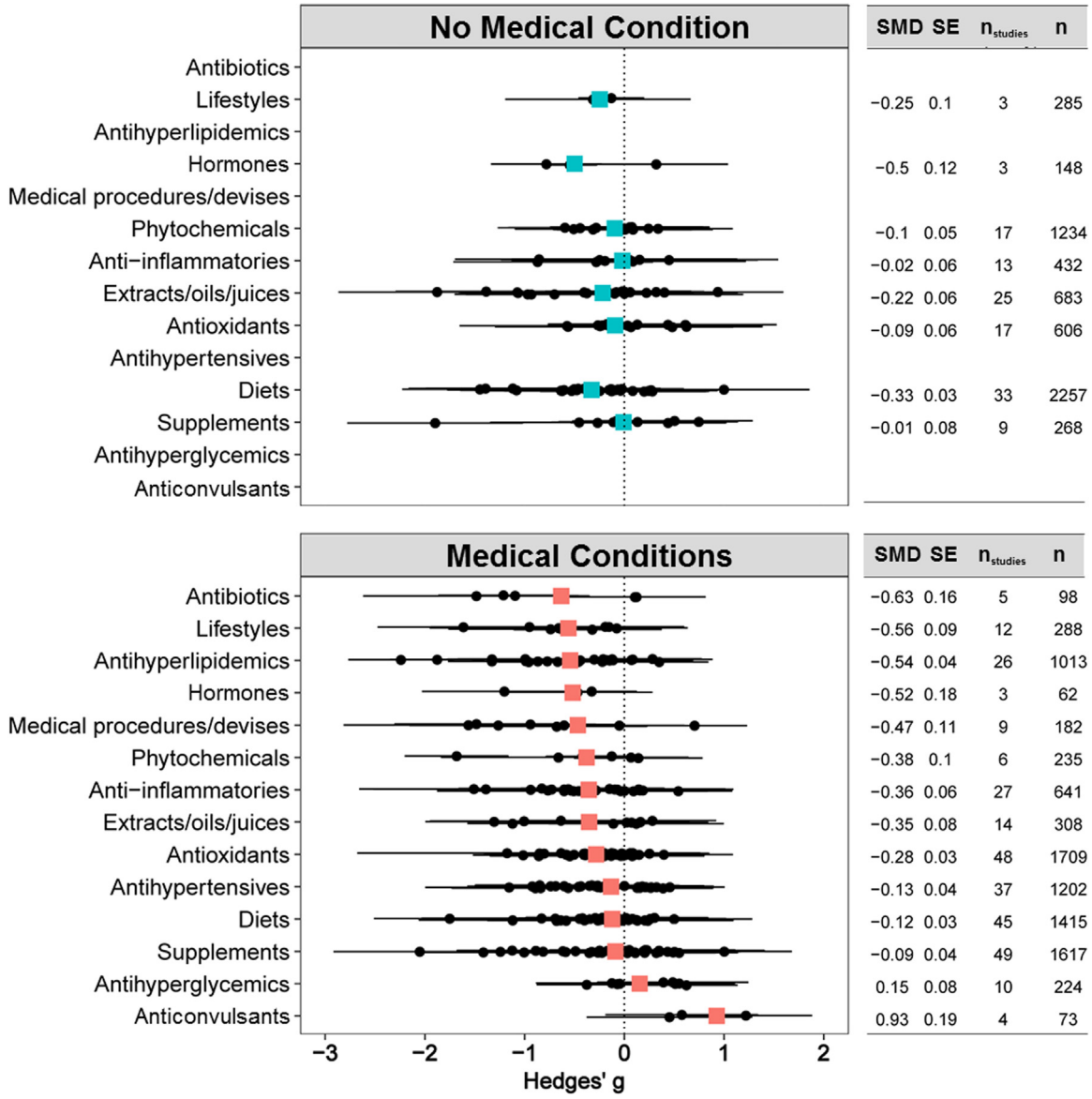

Fig. 2. Effect of different categories of strategies to reduce the levels of 8-iso-PGF$_{2\alpha}$ among populations with and without medical conditions. Scatterplot of the calculated Hedges' value for each strategy as well as the mean per category. A negative Hedges' g indicates a reduction in the levels of 8-iso-PGF$_{2\alpha}$ from the non-treated or placebo group. Black dots with lines are calculated Hedges' g values and 95% confidence interval for each included publication; colored squares are the fixed-effects model estimate for each category. Table abbreviations are: SMD = standardized mean difference (*i.e.*, fixed-effect model estimate for combined Hedges' g), SE = standard error in this estimate, n studies = number of unique publications in each category, n = total number of measured samples per category.

3.2. Total 8-iso-PGF$_{2\alpha}$

In addition to free 8-iso-PGF$_{2\alpha}$, some publications measure the effect of strategies to decrease total 8-iso-PGF$_{2\alpha}$ levels. Total 8-iso-PGF$_{2\alpha}$ is a measure of both the free 8-iso-PGF$_{2\alpha}$ as well as the 8-iso-PGF$_{2\alpha}$ content that is esterified to phospholipids and other membrane lipids. This biomarker, although similar to free 8-iso-PGF$_{2\alpha}$, has potentially distinct generation chemistry and metabolism and, thus must be analyzed separately and not combined with free 8-iso-PGF$_{2\alpha}$ measurements. Available data on total 8-iso-PGF$_{2\alpha}$ are presented as forest plots in Supplemental Figs. 3 and 4 for populations with and without medical conditions, respectively. For the categories with a significant effect and multiple references available, in comparison to free 8-iso-PGF$_{2\alpha}$, the only two categories that were different were the extracts/oils/juices ($g = -0.35$ for free 8-iso-PGF$_{2\alpha}$ and $g = -0.8$ for total 8-iso-PGF$_{2\alpha}$) and supplements ($g = -0.09$ for free 8-iso-PGF$_{2\alpha}$ and $g = -0.4$ for total 8-iso-PGF$_{2\alpha}$) in the non-healthy populations. All others either were the same or too few data were present to make a conclusive determination. No distinction between medical conditions could be made to calculate the effectiveness of strategies to reduce total 8-iso-PGF$_{2\alpha}$ levels due to a lack of multiple studies for most medical conditions.

4. Discussion

Based on the results of the meta-analysis, there are many different methodologies, strategies, medications, and other compounds which can lower levels of 8-iso-PGF$_{2\alpha}$ in humans. The extent of reduction for each of these strategies is dependent on both the treatment itself and the population studied [33,34]. Patrignani et al. [33] were the first to notice this trend for 8-iso-PGF$_{2\alpha}$ in their studies of the effect of vitamin E on 8-iso-PGF$_{2\alpha}$ levels. It was noted that the change in 8-iso-PGF$_{2\alpha}$ levels as calculated by the slope between pre-and post-levels after administration of vitamin E to patients with cystic fibrosis, hypercholesterolemia, and diabetes mellitus type 2, as well as to chronic tobacco

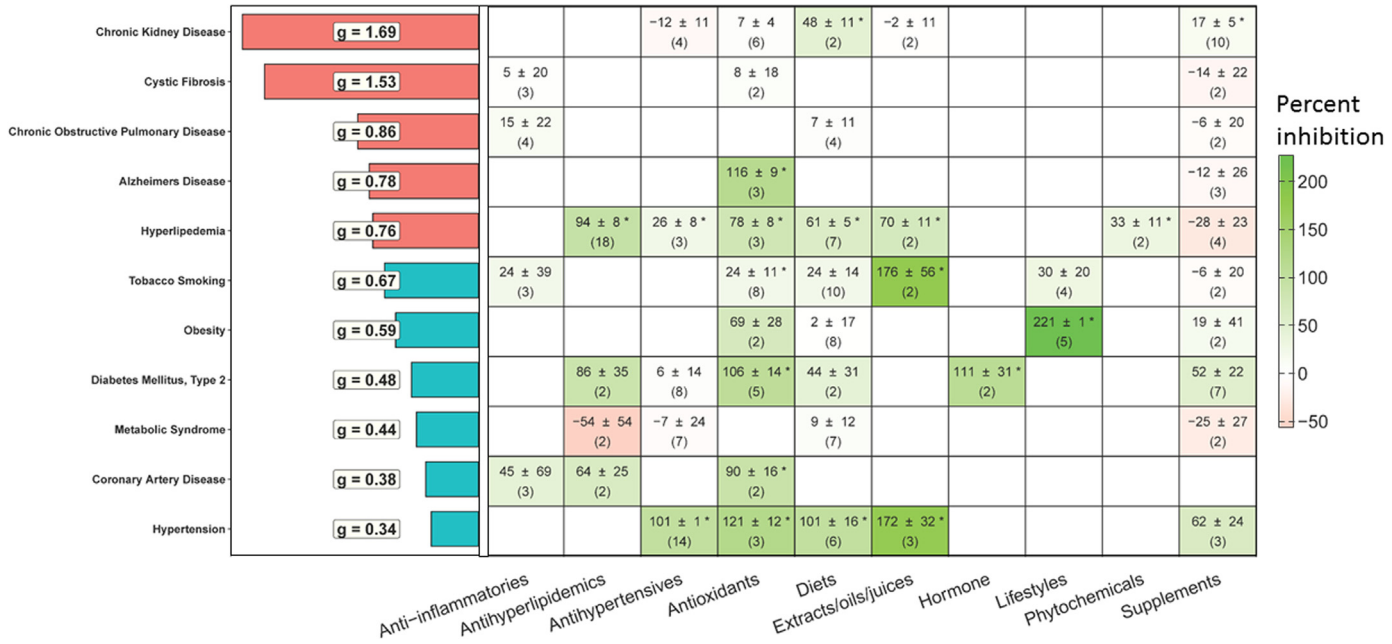

Fig. 3. Effect of different categories of strategies to reduce 8-iso-PGF$_{2\alpha}$ levels stratified by medical condition. Data are presented as percent inhibition ± standard error. Percent inhibition is calculated using **Formula** (1) and is derived from the difference in Hedges' g value for the reduction in 8-iso-PGF$_{2\alpha}$ levels of each strategy and the Hedges' g for elevated 8-iso-PGF$_{2\alpha}$ levels for each medical condition as calculated by van 't Erve et al. [27]. * denotes an effect statistically significantly different from 0.

smokers, was correlated with the elevation of 8-iso-PGF$_{2\alpha}$ levels for each condition [33]. This early work shows that the effectiveness of reduction in 8-iso-PGF$_{2\alpha}$ levels should not be interpreted generally; it is best interpreted in the context of the conditions studied. In the meta-analysis presented here, the confounding effect of medical conditions is very clear in the interpretation of the effectiveness of antioxidants. In populations with no medical condition, the combined Hedges' g for antioxidants is − 0.28 ± 0.03, which is, quantitatively, a small effect (Fig. 2). Based on this result, we could conclude that administration of antioxidants is not an effective strategy to lower 8-iso-PGF$_{2\alpha}$ levels. However, since we are talking about inhibition of an elevated level of 8-iso-PGF$_{2\alpha}$, the Hedges' g value is best interpreted relative to the Hedges' g value of the population on which the strategy was performed. In that case, large effects of near 100% inhibition for many medical conditions are observed, meaning that antioxidants in most cases do significantly reduce the 8-iso-PGF$_{2\alpha}$ levels (Fig. 3). Given this observation, it is important to note that a large majority of studies with dietary interventions and antioxidant therapies where conducted on populations without medical conditions. It was not possible to calculate a relative effectiveness within these populations as there was no increase in 8-iso-PGF$_{2\alpha}$ levels. The reduction in levels seen in these populations could be real reductions or the effect of unreported medical conditions within these populations.

4.1. Caution for mechanism interpretation

With the historical evidence and recent reinforcement of the complex generation mechanism of F$_2$-isoprostanes, especially 8-iso-PGF$_{2\alpha}$ [25,35–44], simple explanations based on historical dogma for the mechanism behind the effect or non-effect of specific strategies should be made with caution. As has been pointed out before [45–47], in addition to affecting formation by scavenging free radicals, 8-iso-PGF$_{2\alpha}$ levels can be manipulated by changes in metabolism, excretion rates, substrate availability, redox-environment, and enzymatic activities of prostaglandin H synthase (PGHS). Besides the classical mechanism [48], antioxidants such as vitamins C and E and other substances can affect the redox-environment by numerous other mechanisms, including signaling, reducing the level of hydrogen peroxide and/or lipid hydroperoxides, all of which are important in healthy cell signaling and enzyme activities. Reducing the peroxide level will reduce the activity of, *e.g.,* prostaglandin-H-synthases, which are potential sources of 8-iso-PGF$_{2\alpha}$ [49–51] *in vivo*. Also, since the majority of F$_2$-isoprostanes are esterified, reducing the total amount of phospholipids by, *e.g.,* weight loss, or decreasing the hydrolysis rate of esterified 8-iso-PGF$_{2\alpha}$ by changes in phospholipase A2 activity would affect free 8-iso-PGF$_{2\alpha}$ levels without altering formation [45,52].

Since there are multiple and controversial mechanisms to explain the effect of each strategy [48,53–59], it is imperative not to over interpret the results presented here and rely purely on the quantitative effect. Future mechanistic studies will need to be performed to ascertain whether the 8-iso-PGF$_{2\alpha}$ measured is formed through a chemical or oxidative stress type pathway or whether enzymatic generation is the primary source [43,44,60]. This distinction, together with studies on the mechanism of each strategy, will provide the comprehensive evidence needed to fully classify the involvement of oxidative stress across human conditions.

4.2. Limitations to the meta-analysis

There are some limitations to the interpretation of this meta-analysis. To simplify the analysis, subjective choices were made to categorize each strategy instead of analyzing them separately. In some categories, especially medications, this categorization is straightforward; however, in other categories, *e.g.,* supplements, extracts, phytochemicals, antioxidants, and others, the categorization could have introduced some bias due to oversimplification. All strategies included in each category are listed in Supplemental Table 1. The most restrictive category was chosen to be antioxidants, which also contains the largest number of references. This category was limited to only treatment with tocopherols (Vitamin E), tocotrienols, ascorbic acid (vitamin C), glutathione, N-acetyl-cysteine, alpha-lipoic acid, or blends of these compounds (*i.e.* antioxidant or nutraceutical blends). Most other strategies claiming that their studied substances are antioxidants were instead classified as extracts/juices/oils (*e.g.,* fish oil or green tea extract) if

they were processed substances, or as supplements or phytochemicals if they were pure substances (*e.g.*, docosahexaenoic acid (DHA) or quercetin).

An additional limitation is overinterpretation due to small sample size. There are several categories (*e.g.,* hormones, medical devices, anticonvulsants, and antibiotics) as well as strategy/medical condition combinations, such as extracts/oils/juice in tobacco smokers or chronic kidney disease, which rely on the minimum of 2 publications describing populations with these conditions. The estimates for these groups and others with few studies are not ideal, but hopefully, with future research, these current estimates can be confirmed and broader interpretation will be possible.

4.3. Conclusion

In conclusion, there are many distinct strategies which can reduce the levels of 8-iso-$PGF_{2\alpha}$ in humans. The largest reductions are seen in populations with a specific medical condition/strategy combination. No general rule on the effectiveness of any given strategy in all medical conditions can be devised. For example, antioxidants do not significantly reduce 8-iso-$PGF_{2\alpha}$ in tobacco smokers and chronic kidney disease but do in several other conditions. Future research should be conservative in the generalization of the effectiveness of new strategies to reduce 8-iso-$PGF_{2\alpha}$ levels and fully investigate the mechanism of generation before making conclusions.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.redox.2018.05.003.

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