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Review

# The role of exercise in minimizing postprandial oxidative stress in cigarette smokers

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## Abstract

Cigarette smoking continues to pose a significant health burden on society. Two well-described mechanistic links associating smoking with morbidity and mortality include elevated blood lipids and increased oxidative stress. These variables have traditionally been measured while an individual is fasting, but evidence suggests that postprandial lipemia and oxidative stress provide more important information concerning susceptibility to disease, in particular cardiovascular disease. Cigarette smokers have elevated levels of biomarkers of oxidative stress at rest and experience impaired postprandial lipid and glucose metabolism. We have confirmed these findings while noting an exaggerated oxidative stress response to high-fat feeding. Smoking cessation is without question the best approach to minimizing smoking-induced ill health and disease, but success rates among those who attempt to quit are dismal. Other means to decrease a smoker's susceptibility to oxidative stress–related disease are needed. We propose that exercise may aid in attenuating postprandial oxidative stress, and we do so in 3 distinct ways. First, exercise stimulates an increase in endogenous antioxidant enzyme activity. Second, exercise improves blood triglyceride clearance via a reduced chylomicron–triglyceride half-life and an enhanced lipoprotein lipase activity. Third, exercise improves blood glucose clearance via an enhanced glucose 4 transport protein translocation and protein content, as well as insulin–insulin receptor binding and postreceptor signaling. Improvements in antioxidant status, as well as lipid and glucose processing, may aid greatly in minimizing feeding-induced oxidative stress in smokers. If so, and in accordance with the recent joint initiative of the American College of Sports Medicine and the American Medical Association, exercise may be viewed as a "medicine" for cigarette smokers at increased risk for postprandial oxidative stress. Research into this area may provide insight into the potential benefits of exercise for this purpose.

## Introduction

Cigarette smoking remains a significant health burden within the United States, accounting for approximately 438,000 deaths each year (Centers for Disease Control and Prevention [CDC], 2005a). A large number of these deaths are attributed to cardiovascular disease (CVD), in particular coronary heart disease (Leone, Giannini, Bellotto, & Balbarini, 2004) and stroke (Hankey, 1999). In addition, the economic cost of CVD treatment alone in the United States in 2005 has been estimated at $393.5 billion, a substantial portion of which can be attributed directly to cigarette smoking (Max, 2001). According to the CDC (2005b), approximately 20.9% of adults (44.5 million) in the United States are cigarette smokers. Two well-described mechanistic links associating smoking with CVD morbidity and mortality include elevated blood lipids (Gould, Davies, Alemao, Yin, & Cook, 2007) and oxidative stress (Burke & Fitzgerald, 2003).

In living cells, reactive oxygen species (ROS) are continuously formed as a consequence of normal cellular metabolism and can be elevated during periods of environmental stress (Halliwell, 1984). Production of ROS in quantities that overwhelm the antioxidant defense system is termed oxidative stress. Chronic oxidative stress has a strong association with multiple CVDs (e.g., atherosclerosis, hypertension, and stroke), in which common molecular pathways related to pathogenesis and progression have been identified and presented in detail (Ross, Stagliano, Donovan, Breitbart, & Ginsburg, 2001). Several reviews of associated mechanisms relating oxidative stress with CVD have been presented (Ceriello & Motz, 2004; Chen & Mehta, 2004; Griendling & FitzGerald, 2003a, 2003b; Ogita & Liao, 2004; Stocker & Keaney, 2004).

Increased production of ROS is a potentially important mechanistic link between tobacco use and disease (Ambrose & Barua, 2004; DeMarini, 2004; Ross et al., 2001). Many of the more than 4,000 chemical compounds present in tobacco promote ROS formation and pose a significant oxidant stress in vivo (Church & Pryor, 1985). Cigarette smokers have elevated resting biomarkers of oxidative stress such as F2-isoprostanes (Morrow et al., 1995), malondialdehyde (Bloomer, 2007; Ozbay & Dulger, 2002; Sharma et al., 2005), and protein carbonyls (Kirkham, Spooner, Rahman, & Rossi, 2004; Pignatelli et al., 2001), compared with nonsmokers. These findings may be partly due to lower circulating antioxidants, which are often

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depleted by the toxicants present in tobacco, and lower in smokers compared with nonsmokers (Alberg, 2002; Bloomer, 2007; Dietrich et al., 2002; Kilinc, Okur, Kurutas, Guler, & Yildirim, 2004). Oxidation of these important macromolecules can lead to loss of membrane stability and fluidity (e.g., lipid peroxidation products), loss of catalytic or structural function (e.g., protein oxidation products), and increased potential for mutagenesis (e.g., DNA oxidation products). The oxidation of low-density lipoprotein (LDL) cholesterol presents a cytotoxic environment, often promoting endothelial dysfunction and impaired nitric oxide biosynthesis (Jialal, 1998; Norata, Tonti, Roma, & Catapano, 2002), ultimately leading to vascular dysfunction. Furthermore, oxidized LDL may promote platelet adhesion, trigger DNA strand breaks, and promote apoptosis, all of which contribute to the development of atherosclerotic disease (Sachidanandam, Fagan, & Ergul, 2005). Although the degree of atherosclerosis is certainly important, most clinical events such as myocardial infarction and stroke appear precipitated by rupture of atherosclerotic plaque, in which ROS also are involved (Sugiyama et al., 2001). The evidence is clear that cigarette smoking leads to elevated oxidative stress, which plays an important role in the pathogenesis and progression of CVD.

The above-cited findings are typically observed while an individual is fasting. Increasing evidence suggests that postprandial lipemia (increased blood triglycerides [TAG]) and oxidative stress provide more important information concerning susceptibility to CVD (Albright et al., 2000; O'Keefe & Bell, 2007; Pastromas, Terzi, Tousoulis, & Koulouris, 2008). For example, randomized controlled trials indicate that reducing postprandial lipemia appears to significantly slow atherosclerotic progression and may improve long-term cardiovascular prognosis (O'Keefe & Bell, 2007). In addition, postprandial elevations in blood TAG are correlated directly with the increase in superoxide radical (Bae et al., 2001), a ROS that is believed to be produced directly by vascular endothelial cells (Brownlee, 2005; Ceriello & Motz, 2004).

It is well documented that, although many cigarette smokers may have clinically normal levels of blood lipids (Axelsen et al., 1995) when measured in a fasting state, they experience impaired postprandial lipid metabolism (Axelsen et al., 1995; Eliasson, Mero, Taskinen, & Smith, 1997). The impairment in TAG processing is related to an increased chylomicron–TAG half-life, in addition to decreased activity of lipoprotein lipase (LPL), the rate-limiting enzyme for serum TAG removal (Mero, Syvanne, Eliasson, Smith, & Taskinen, 1997). We have confirmed these findings and noted an exaggerated oxidative stress response to high-fat feeding in smokers compared with nonsmokers (Bloomer, Solis, Fisher-Wellman, & Smith, 2008). This was the first study to assess the oxidative stress response to feeding in a sample of smokers. In a prior investigation using nonsmokers, we noted significant correlations between TAG and common oxidative stress biomarkers such as malondialdehyde ($r = .55$, $p < .00001$), hydrogen peroxide ($r = .67$, $p < .00001$), and protein carbonyls ($r = .18$, $p = .02$). These findings are in agreement with other work involving nonsmokers, indicating strong associations between postprandial TAG and oxidative stress (Anderson et al., 2001; Bae et al., 2001; Tushuizen et al., 2006). From a mechanistic view, blood TAG increases in response to a high-fat feeding (Anderson et al., 2001; Bae et al., 2001; Tsai, Li, Lin, Chao, & Chen, 2004; Tushuizen et al., 2006), and this increase in circulating TAG promotes a robust increase in superoxide radical (Bae et al., 2001; Mohanty et al., 2002). This increase in superoxide promotes the oxidation of important macromolecules, such as lipids (Neri et al., 2005; Tushuizen et al., 2006; Bloomer, Ferebee, Fisher-Wellman, Quindry, & Schilling, manuscript submitted for publication) and proteins (Nadeem, Raj, & Chhabra, 2005), while impairing nitric oxide biosynthesis and availability (Neri et al., 2005; Vassalle, Lubrano, L'Abbate, & Clerico, 2002; Weiss et al., 2004). The combined impact of macromolecule oxidation, which impairs cellular function (Valko et al., 2007), coupled with decreased nitric oxide bioavailability, which impairs smooth muscle cell relaxation (Collier & Vallance, 1991), negatively alters vascular health and function (Cai & Harrison, 2000).

Due to defects in lipid metabolism, coupled with increased ROS production from cigarette smoke exposure, smokers experienced exaggerated postprandial oxidative stress (Bloomer et al., 2008). While our initial work is the only study to date to directly demonstrate this interaction (Bloomer et al., 2008), the robust increase in oxidative stress biomarkers in smokers deserves attention. Considering that smokers have impaired lipid metabolism (Axelsen et al., 1995; Eliasson et al., 1997) leading to elevations in circulating TAG, and circulating TAG is strongly associated with superoxide production (Bae et al., 2001), our findings of elevated postprandial oxidative stress in smokers compared to nonsmokers are not surprising. Additional study related to the interaction of lipemia and oxidative stress in smokers is needed.

Besides impaired lipid metabolism, smokers often have impaired glucose metabolism, which appears related to defects in insulin sensitivity, signaling, and glucose 4 transport protein (GLUT4) translocation (Eliasson, 2003). As with postprandial increases in TAG, the increase in blood glucose is associated with increased endothelial cell superoxide production (Yano et al., 2004). This is particularly apparent when individuals are fed a highly processed carbohydrate meal, as oxidative stress has been shown to increase as a function of the magnitude and rate of glucose entry into circulation (Monnier et al., 2006). Smokers are notorious for consuming diets high in processed carbohydrates and saturated fat (Bloomer, 2007; Palaniappan, Jacobs Starkey, O'Loughlin, & Gray-Donald, 2001) and low in antioxidant-micronutrient–containing foods (Birkett, 1999; Bloomer, 2007; Ma, Hampl, & Betts, 2000; Northrop-Clewes & Thurnham, 2007; Palaniappan et al., 2001). Such poor dietary habits, coupled with impaired endogenous antioxidant defense due to routine exposure to cigarette smoke (Alberg, 2002; Dietrich et al., 2003; Zhou et al., 2000), predispose smokers to increased oxidative stress, as we have demonstrated (Bloomer et al., 2008).

The logical question then becomes, "So what can be done to decrease the degree of postprandial oxidative stress in cigarette smokers?" The single best approach is smoking cessation. Not only would this decrease fasting levels of ROS (Oguogho, Lupattelli, Palumbo, & Sinzinger, 2000; Pilz et al., 2000) and possibly improve lipid and glucose metabolism in response to feeding (as elevated fasting TAG and glucose levels are commonly observed in smokers; Imamura et al., 1996; Willett et al., 1983; Willi, Bodenmann, Ghali, Faris, & Cornuz, 2007), but also it would result in an improvement in the endogenous antioxidant

defense system (Jatuporn et al., 2003; Lane, Opara, Rose, & Behm, 1996; Polidori, Mecocci, Stahl, & Sies, 2003), indicating a greater ability of the body to defend against ROS production. Despite these promising outcomes, one major problem remains: the success of smoking cessation is extremely poor. For example, approximately 46% of smokers in the United States attempt to quit each year, but only 7% of those who attempt to quit are successful for at least 1 year (Fiore et al., 2000). Based on this rather grim reality, other methods to decrease smokers' susceptibility to postprandial oxidative stress and related disease are needed.

The role of exercise to minimize postprandial oxidative stress in smokers. A method that has not been investigated in smokers, with the exception of our pilot study as described below (Bloomer & Fisher-Wellman, manuscript submitted for publication), is regular exercise. Both acute and chronic exercise may aid in attenuating postprandial oxidative stress in three distinct ways, with the following mechanisms well documented for nonsmokers. Although resistance and anaerobic exercise have been shown in a few studies to positively impact fasting levels of antioxidant defense markers, as well as blood glucose and lipids, the majority of work related to postprandial assessments has included aerobic exercise (e.g., walking, jogging, cycling). Therefore, the following text is specific to this form of exercise.

First, exercise results in an increase in endogenous antioxidant enzyme activity (Ji, 2002) as well as nonenzymatic antioxidants such as glutathione (Ji, 2002) and other plasma thiols (Metin, Gumustas, Uslu, Belce, & Kayserilioglu, 2003). Acute exercise gives rise to an increased production of ROS, leading to the activation of certain antioxidant enzymes (e.g., glutathione peroxidase, glutathione reductase, superoxide dismutase, catalase), which protect against potential oxidative damage. This process is illustrated by several studies reporting transient changes in the antioxidant defense system following a variety of aerobic exercise protocols (Akova et al., 2001; Buczynski, Kedziora, Tkaczewski, & Wachowicz, 1991; Elosua et al., 2003; Fatouros et al., 2004; Inayama et al., 2002; Kanaley & Ji, 1991; Vider et al., 2001). Although the components of the defense system are quenched temporarily and often cannot completely prevent oxidative damage, the exercise-induced increase in ROS appears to be a necessary "signal" for the upregulation of the antioxidant defense system, in turn providing protection from future pro-oxidant insult. This process is likely a result of ROS-induced activation of the redox-sensitive transcription factor nuclear factor kappa B, which upon activation leads to the expression of certain antioxidant enzymes (Gomez-Cabrera et al., 2005), as an upregulation in antioxidant enzymatic activity has been reported following regular endurance training (Elosua et al., 2003; Fatouros et al., 2004; Miyazaki et al., 2001; Ohno, Yahata, Sato, Yamamura, & Taniguchi, 1988). Moreover, greater antioxidant defense has been shown to result in lower postprandial oxidative stress (Ceriello et al., 2002).

Second, exercise improves blood TAG clearance via a reduced chylomicron–TAG half-life, an enhanced LPL activity (Thompson, Cullinane, Henderson, & Herbert, 1980), as well as a reduction in fasting TAG levels (Cohen, Noakes, & Benade, 1989). Acute exercise has been shown to result in a decreased postprandial TAG when performed prior to (Barrett, Morris, Stensel, & Nevill, 2006; Gill et al., 2004; Katsanos & Moffatt, 2004; Kolifa, Petridou, & Mougios, 2004; Miyashita, Burns, & Stensel, 2006; Petridou et al., 2004) and following (Katsanos & Moffatt, 2004; Mc Clean et al., 2007) meal ingestion. Moreover, the degree to which TAG is attenuated following feeding may be related to the timing of exercise (Petridou et al., 2004), as one report indicates that the increase in LPL activity may be delayed following acute exercise for up to several hours (Kiens, Lithell, Mikines, & Richter, 1989). It is unclear which of these mechanisms is primarily responsible for the reduction in postprandial TAG levels observed in trained compared with sedentary individuals, but differences are likely related to a combination of the factors. Repeated exposure to the increased activation of LPL resulting from regular acute exercise appears to result in an upregulation in LPL activity (Kantor, Cullinane, Sady, Herbert, & Thompson, 1987). The increase in LPL at rest and a reduction in chylomicron–TAG half-life, coupled with TAG's ability to be used as a fuel source during exercise, are potential mechanisms responsible for the observed decrease in fasting TAG levels observed in trained individuals (Cohen et al., 1989). Moreover, any reduction in fasting TAG could potentially result in an attenuation of postprandial oxidative stress, as the magnitude of the oxidative stress response has been shown to be highly correlated to fasting TAG levels (Bae et al., 2001; Bloomer et al., manuscript submitted for publication).

Third, exercise improves glucose clearance via an enhanced insulin–insulin receptor binding and postreceptor signaling (Wojtaszewski et al., 1999), as well as an enhanced GLUT4 translocation (Henriksen, 2002). This effect is particularly noticed with specificity to high-carbohydrate feedings independent of high dietary fat (Monnier et al., 2006). For mixed meals containing a combination of fat and carbohydrate, enhanced lipid metabolism appears most important, as the blood glucose response to high-fat feeding is minimal (Blendea, Bard, Sowers, & Winer, 2005; Bloomer et al., 2008). Acute exercise results in the translocation of GLUT4 transport proteins from the intracellular housing environment to the cell membrane surface, where they facilitate glucose entry into the cell in a non–insulin-dependent fashion (Kraniou, Cameron-Smith, & Hargreaves, 2006). A transient increase in GLUT4 mRNA has been reported following acute exercise, which usually normalizes 24 hr after exercise (Kraniou et al., 2006). The adaptive increase in skeletal muscle GLUT4 protein arises from repeated, transient increases in GLUT gene transcription following each exercise bout (Kraniou, Cameron-Smith, & Hargreaves, 2004). Similar to mechanisms discussed above relative to TAG, a reduction in fasting glucose with regular exercise via increased activity of GLUT4, as well as an increase in insulin sensitivity, could potentially attenuate postprandial oxidative stress. Evidence indicates that oxidative stress is increased in insulin-resistant subjects compared with healthy control subjects (Ceriello et al., 2002), and cigarette smokers are known to have symptoms of insulin resistance.

Using a cross-sectional design, we recently studied postprandial oxidative stress and TAG in exercise-trained and sedentary cigarette smokers fed a high-fat meal (Bloomer et al., manuscript submitted for publication). We noted slightly higher antioxidant enzyme activity (superoxide dismutase, catalase, and glutathione peroxidase) in the trained smokers, as well as attenuated lipid peroxidation in the trained compared with

sedentary smokers at 4 and 6 hr after the meal. A limitation of the study was its cross-sectional design, which precluded us from controlling the exercise stimulus. Moreover, trained smokers reported performing only 2–3 hr of exercise per week, and the intensity was relatively low. Therefore, it is possible that more robust effects would be noted if exercise was performed at a higher volume and intensity, in a controlled environment.

## When and how should the exercise be done?

The effects of acute exercise (in particular as related to TAG) are known to persist for up to 16 hr (Katsanos, 2006); however, these effects may be most pronounced during the first few hours after exercise. Therefore, although chronic exercise performed 3–4 days/week may be adequate to attenuate postprandial oxidative stress outside of the context of a single exercise bout, more pronounced attenuation may be observed with acute exercise bouts. If so, more frequent exercise may be necessary to result in the desired outcome. This suggestion for frequent (e.g., daily) exercise sessions is the same recommendation provided for the medical management of diabetes (Albright et al., 2000) and is possible for most individuals. Considering that the effects are generally observed for periods of 16 hr after exercise and that meals are usually consumed during early morning to evening hours, suggesting that smokers engage in regular morning exercise bouts, seems most reasonable.

Within the context of the exercise bout itself, the stimulus must be of adequate intensity and duration for such effects to occur. For example, exercise of moderate intensity (~50%–70% $VO_{2max}$) has been shown to improve postprandial TAG clearance (Katsanos, 2006). Exercise performed at 60% $VO_{2peak}$ for 45 min has been reported to decrease postprandial TAG by 31% (Zhang, Ji, Fretwell, & Nunez, 2006). McClean et al. (2007) noted attenuation in TAG and lipid peroxidation in healthy participants when exercising for 60 min at 60% maximum heart rate, which is roughly equivalent to only 50%–55% $VO_{2peak}$. Increases in GLUT4 and GLUT4 mRNA observed following exercise have been shown to respond in a similar fashion despite the use of different intensity protocols (approximately 40% and 80% $VO_{2peak}$, respectively) that were matched for total work (Kraniou et al., 2006). Furthermore, adaptation in the antioxidant defense system appears to occur following endurance training at an intensity of greater than 60% $VO_{2max}$ (Elosua et al., 2003; Fatouros et al., 2004). Therefore, moderate exercise intensity should be necessary. Such moderate exercise corresponds to a heart rate equivalent to roughly 60% of maximum predicted heart rate ([220 − age] × 0.6) and to a subjective rating of "somewhat hard" (Bloomer, Goldfarb, Wideman, McKenzie, & Consitt, 2005). This level of exercise is certainly reasonable for most otherwise healthy, sedentary to moderately active smokers to perform on a regular basis.

Besides exercise intensity, energy expenditure is also related to exercise duration. Murphy, Nevill, and Hardman (2000) found that untrained participants need to expend approximately 350 kcal to significantly attenuate postprandial TAG. Therefore, exercise duration of roughly 45 min should be sufficient to allow for positive changes in untrained smokers, based on energy expenditure analyses from our previous work using aerobic exercise (Bloomer et al., 2005; Bloomer, Davis, Consitt, & Wideman, 2007).

Although the above considerations apply specifically to a single bout of exercise, if performed on a regular basis, or as part of an intervention study, the frequency should be maintained for at least 3 days/week. The intensity and duration can be progressed according to the guidelines of the American College of Sports Medicine, beginning at 55% maximum heart rate for 30 min and progressing to higher levels over time (e.g., 80% maximum heart rate for 45–60 min; Whaley, 2005). As a component of a research study, this level should be maintained for 8–10 weeks, given that this volume and intensity of exercise for this period of time should result in favorable changes in TAG (Cohen et al., 1989) and glucose (Borghouts & Keizer, 2000) processing, as well as increased antioxidant status (Ji, 2002). For both acute and chronic exercise bouts in a research setting, it is extremely important that the intensity (monitored specifically via heart rate) and duration of exercise be supervised. These variables should be documented by the investigators to ensure participant compliance.

## Considerations in research design: exercise timing, test meals, and sample size

In relation to the test meal and the associated outcome measures, participants should refrain from any strenuous physical tasks during the 24-hr period prior to each test meal because acute exercise may affect postprandial TAG (Katsanos, 2006) and glucose (Larsen, Dela, Madsbad, & Galbo, 1999) for several hours. At the same time, because a detraining effect may take place with as little as 60 hr of inactivity (Herd, Hardman, Boobis, & Cairns, 1998), if involved in an exercise intervention study, participants should not be inactive for any longer than this time following the final exercise session. Otherwise, the chronic effects of exercise may not be as apparent. Indeed, timing of the test meals is crucial in such an investigation.

In most studies, the meals have consisted of pure carbohydrate (e.g., glucose: Lee, Kim, & Bae, 2002; Miyazaki et al., 2007; Mohanty et al., 2000; Serin, Konukoglu, Firtina, & Mavis, 2007; Weiss et al., 2004), pure fat (e.g., whipping cream: Mohanty et al., 2002), whole food or liquid mixed macronutrient meals (e.g., sandwich: Gopaul, Zacharowski, Halliwell, & Anggard, 2000; Schinkovitz, Dittrich, & Wascher, 2001; Tushuizen et al., 2006; milkshake: Bloomer et al., 2008; McClean et al., 2007), or pure protein (e.g., casein: Mohanty et al., 2002). All such meals result in oxidative stress, with the lipid-rich meals contributing to the rise in blood TAG and the glucose-rich meals yielding a rise in blood glucose. The peak response for blood TAG and oxidative stress markers is typically 3–4 hr after the meal, highlighting the need for repeated blood sampling during the 4- to 6-hr postprandial period. Participants should be tested in the morning following an overnight fast (minimum of 10 hr), and antioxidant intake from whole food should be assessed, as this can influence the degree of macromolecule oxidation in cigarette smokers (Kelly, 2002a, 2002b, 2003). No food, calorie-containing beverages, or cigarettes should be allowed during the postprandial observation period.

Due to the large effects for blood glucose, TAG, and lipid peroxidation observed in previous work on the effect of exercise on postprandial oxidative stress in nonsmokers (Gill et al., 2004; Katsanos & Moffatt, 2004; McClean et al., 2007; Tsetsonis,

Hardman, & Mastana, 1997), relatively small samples are necessary in such studies. For example, if investigating the effects of acute exercise on postprandial oxidative stress using a crossover design (acute exercise or no acute exercise prior to meal consumption), a conservative sample size of 20 participants would be adequate to detect significant effects for outcome measures assuming a Type I error of .05 (two tailed) and a Type II error of .20. Based on data from previous exercise intervention studies, a total sample size of 40 participants (randomized to either a no exercise or an exercise intervention) would be adequate to detect significant effects for outcome measures assuming a Type I error of .05 (two tailed) and a Type II error of .20. Therefore, such studies do not appear cumbersome to perform.

## Discussion

We have presented information related to the potential role of exercise as a therapeutic agent to attenuate postprandial oxidative stress in cigarette smokers, as well as potential guidelines to consider in planning such investigations. Although limited data are available related to this topic, it is possible that exercise can have a favorable impact on postprandial oxidative stress in smokers. If studies support this hypothesis, greater emphasis may be placed on regular exercise for cigarette smokers, in an attempt to minimize health consequences related to oxidative stress. As of now, a specific and firm recommendation for the performance of regular exercise for cigarette smokers does not exist.

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## Declaration of Interests

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