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Review Article

Effect of Different Environmental Exposures on Retinal Arteriolar and Venular Diameters in Healthy Individuals and Those with Increased Cardiovascular Risk: A Systematic Review

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Abstract

Context: Fundus scanning has emerged as a non-invasive way to estimate the risk for cardiovascular diseases. Research suggests that environmental risk factors, such as diet and smoking, influences the structure of the retinal microvasculature, particularly the central retinal arteriolar and venular equivalents (CRAE & CRVE).

Objective: This systematic review provides an updated overview of existing research on the effect of diet, smoking, physical activity, air pollution, alcohol consumption and miscellaneous exposures on retinal microvasculature in healthy individuals and people at risk for cardiovascular disease.

Data Sources: The databases PubMed, Web of Science, OVID were used as data sources and were last accessed September 12nd 2024.

Study Selection: Peer-reviewed studies investigating the effect of any type of environmental exposure on retinal microvessel diameters in healthy individuals and people at risk for cardiovascular disease were included.

Data Extraction: Relevant information and outcomes of 88 studies were extracted. Methodological quality was assessed using the NIH quality assessment tool. Data from each included study was extracted by two independent reviewers, while a third reviewer checked for consensus.

Conclusions: Several dietary components, including numerous phytochemicals or fish oils have beneficial effects while other components (high glycemic index products, red meat) have deleterious effects on the retinal microvasculature. There was no unilateral association between smoking and CRAE nor CRVE. A decrease in retinal vessel diameters is induced by isometric exercise, whereas endurance exercise causes increased diameters. Fine Particulate Matter ($PM_{2.5}$) exposure induces decreases in CRAE and CRVE. Further research is necessary to attain scientific consensus on the effects of alcohol consumption on the retinal microvasculature.

Keywords: Retinal Microvasculature, Diet, Smoking, Physical Activity, Air Pollution

Introduction

With an estimated 10% of premature mortality, Cardiovascular Diseases (CVDs) are currently one of the most prevalent diseases globally and the leading cause of death [1]. CVDs are a class of diseases of the heart and blood vessels including coronary heart disease, cerebrovascular disease, stroke, peripheral arterial disease and other conditions related to the heart and blood vessels [1]. Environmental exposures, such as diet, physical activity and air pollution are known to modulate the development and progress of CVD. Exposures that are known to negatively affect the cardiovascular system include cigarette smoke chemicals, air pollutants, high consumption of triglycerides, and sedentary behavior. Specifically, exposure to high levels of fine particulate matter ($PM_{2.5}$) is associated with increased risk of ischemic heart disease, arrhythmias, heart failure and cardiac arrest [2]. In addition, individuals with high triglyceride-glucose index (TyG index) have a higher risk of early-onset stroke compared to individuals with lower TyG index [3]. In contrast, several dietary components, such as certain phytochemicals, fish oils and whole grains, appear to be of great importance in the prevention of cardiovascular disease [4]. For instance, consumption of the Mediterranean diet, rich in polyphenols, carotenoids and fish oils, is associated with reduced risk of CVD [5]. Besides diet, studies suggest that frequent exercise also reduces the risk of CVD [1]. Recent data propose that the effects of several environmental exposures on the development and prevention of CVDs may be mediated via the microcirculation [6]. For this

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reason, the structural changes in microvasculature can be used as an indicator for risk of environmental exposures on subsequent CVD development. The retinal microvasculature is a particularly clinically useful indicator since it can be easily and non-invasively imaged using fundus photography [7].

Fundus photography allows acquisition of retinal measures that provide insight into the state of the microvasculature. Retinal vessel diameters can be computed into the Central Retinal Venular Equivalent (CRVE) and Central Retinal Arteriolar Equivalent (CRAE) parameters. CRAE and CRVE reflect the average width of the retinal arterioles and venules, respectively. Previous studies widely suggest that retinal arteriolar narrowing and venular widening are associated with increased risk of ischemic heart disease and hypertension, the latter being one of the most influential risk factors for developing nearly all forms of CVD [8,9]. The quotient of CRAE and CRVE results in the so-called Arterio-Venous Ratio (AVR). This ratio is negatively associated with CVD risk [10].

A comprehensive understanding of the effect of environmental factors on these retinal microvascular parameters would especially be useful for the field of public health.

Retinal microvascular diameter parameters are clinically relevant and non-invasive biomarkers for systemic cardiovascular health [7-9]. Hence, investigating the modulation of these parameters by environmental exposures underpins scientific understanding of how these factors affect cardiovascular health. These findings can substantiate preventive healthcare aiming to ameliorate cardiovascular health and decrease the prevalence of cardiovascular disease on a population level. In practice, these insights may be incorporated into lifestyle coaching and health education, or converted into public health policies.

A number of reviews have provided an overview of the effect of different environmental exposures on retinal microvasculature. However, previous published reviews focused solely on the relationship between the retinal microvasculature and physical activity, sedentary behavior and adiposity [11] or the relationship between dietary patterns and the retinal microvasculature [12].

Moreover, a review covering the effect of the majority of environmental exposures on the retinal microvasculature was already published over ten years ago by Serre *et al* (2012). However, studies on alcohol consumption were not included [6]. Since then, additional research papers have been published investigating the effect of different types of exposure on the retinal microvasculature. Therefore, the current systematic review will provide an up-to-date overview of published research on the effect of environmental exposures on the retinal microvasculature in healthy individuals.

Methods

Eligibility Criteria

This systematic review is in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [13].

The Population, Intervention, Comparison, Outcomes and Study design (PICOS) search tool was used as a framework to specify the eligibility criteria. Inclusion and exclusion criteria, according to the PICOS format, are presented in Table 1. Included were Randomized Controlled Trials (RCT), Non-Randomized controlled Studies (NRS), case-control, cohort, and cross-sectional studies that aimed to investigate the effect of environmental exposures on the retinal microvasculature in healthy individuals. For a study to be eligible, it should include retinal microvessel caliber/diameter/width measurements, and specific outcome parameters CRAE, CRVE, and AVR. Studies were excluded if they included diseased humans or animals, did not investigate the effect of environmental exposures on the retinal microvasculature, or were not published in English.

Search Strategy

Studies were retrieved from three online databases: PubMed, Web of Science and OVID. All three databases were accessed on September 12th 2024. The identification of keywords was based on the components of the research question and synonyms of the terms. The search terms included in each database are specified in Supplementary data file 1. In all databases, the search terms were split up between ‘Retina’, ‘Exposure’ and ‘Human’. The search in PubMed was further divided into the MeSH terms search, the free text term search and the combined search.

Search Procedures

Search queries can be found in Supplementary data file 1. Searches on the three databases PubMed, Web of Science and OVID yielded 9689 results. Duplicates were removed using Endnote X9.3.3 (Clarivate Analytics, Philadelphia, PA, USA), and Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Duplicates (n= 2695) were removed, leaving 6994 articles for screening. Based on title and abstract, 6789 studies were removed as they did not meet the PICOS inclusion criteria (Table 1). Each article was independently screened by two reviewers. Subsequently, 205 studies were full-text screened for eligibility, after which 117 articles were excluded. Most common reasons for exclusion were outcomes not related to parameters for microvasculature structure, no inclusion of environmental exposures or no full text of the article available. Finally, 88 articles met the inclusion criteria and were included in this review. Full-text eligibility screening for each article was performed independently by two reviewers. Two additional

Table 1: PICOS criteria for inclusion and exclusion of studies (Higgins et al.,2022)[14]

PICOS component	Inclusion criteria	Exclusion criteria
Population	Healthy individuals (no age constraints) and population-based studies including people at risk (people with diabetes type 2, hypertension and/or obesity)	Animals, studies with merely a diseased population
Intervention/ Exposure	Environmental exposure (diet, physical activity and other lifestyle factors, air pollution)	No inclusion of environmental exposure (e.g. studies on blood pressure and genetic influences)
Comparators	Participants less/more/not exposed to analysed environmental exposure	N/A
Outcome	Structural parameters related to retinal microvessel caliber/width/diameter (CRAE, CRVE, AVR)	Outcome that is not a parameter of the retinal microvasculature structure (Glaucoma incidence, Flicker-light response)
Study design	RCTs, prospective and retrospective Cohort, Case-Control, Cross-Sectional studies, Non-Randomized Intervention Studies (NRS)	Review articles, meta-analyses, case reports, unpublished and not peer-reviewed literature

studies that met all requirements but did not show up in the search have been added manually to complement the review.

Data Collection and Quality Assessment

From the 90 eligible studies, information on type of exposure, outcome parameters for retinal microvasculature, and study population was retrieved during extraction. The screening of the title and abstract, the review of full text and data extraction were conducted in Covidence (Covidence, n.d) [15]. For each article, data extraction was independently carried out by two reviewers and confirmed by a third reviewer to ensure inter-rater reliability.

The methodological quality assessment of the eligible article was evaluated by four reviewers. Each article was independently assessed by two reviewers. To ensure inter-rater reliability, a third reviewer confirmed the assessment. The eligible articles were evaluated using the National Institutes of Health (NIH) Quality Assessment tools [15]. The assessment tools were used for observational and intervention studies. Cross-sectional, cohort, randomized controlled trial, case-control and pre-post intervention with no control group studies were evaluated with the NIH Quality Assessment tool for experimental or observational studies. The NIH Quality Assessment tools consisted of either 12 or 14 questions where the answer could be 'yes', 'no', 'cannot determine', 'not reported' or 'not applicable'. The answers on these questions were a representation of the internal validity of the study. Risk of potential selection bias, information bias and confounding were considered. Each study design had a different list of questions specified on their design. Additionally, a classification system has been made to rate a study as 'good', 'fair' or 'poor'. The assessment tools, classification system and outcome of the quality assessment can be found in supplementary data file 3.

Results

In total, 90 papers were eligible for review. The key characteristics of the studies are summarized in Supplementary data file 2. A majority of articles included results on diet (n=28), smoking (n=25) and physical activity (n=28). Several articles reported findings on air pollution (n=7), or alcohol consumption (n=9). The remaining two articles were categorized under miscellaneous environmental exposures, and were about exposure to radiation and working night shifts. Several articles included analyses on multiple environmental exposures.

Diet

The effect of diet and dietary components on the retinal microvasculature was investigated in 28 articles, which included cross-sectional analyses (n=17), prospective cohort studies (n=5) and randomized trials (n=6) of which one had a cross-over design. The studies were conducted in European countries (n=13), Australia (n=11), USA (n=2) and South-East Asian countries (n=2). The assessment of the quality of the studies resulted in good (n= 8), fair (n=19) and poor (n=1).

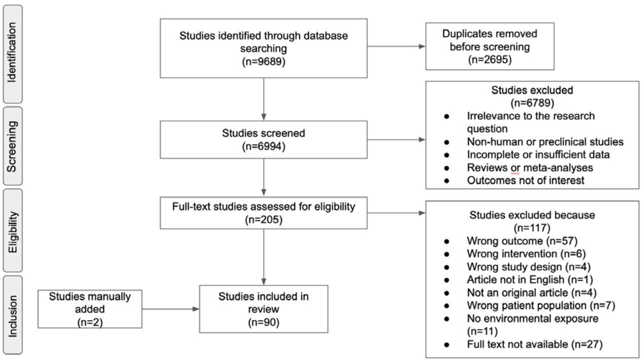

Figure 1: PRISMA flowchart for the systematic review detailing the database search.

The majority (n=21) was published in the last 10 years (2013 or later). Dietary components included carbohydrates (fiber), antioxidants (vitamin A and C, alpha-tocopherol and beta-carotene), fatty acids and proteins. In the majority of the studies both males and females were included, however, certain studies only investigated the effect of diet on the retinal microvasculature in males (n=4). The studies were performed on adults as well as on children. Three studies only included (pregnant) women aged 18 years and older [17-19].

Two large cross-sectional analyses in Australia and Ireland revealed that adherence to a healthy dietary pattern was associated with wider retinal arterioles and narrower retinal venules, while adherence to an unhealthy dietary pattern was associated with the opposite [17,20]. According to the Irish Nun Eye Study, performed in 1233 women older than 55 years old with a restricted lifestyle (dietary and lifestyle limitations), an unhealthy dietary pattern high in dairy products, sugar and salts was associated with wider retinal venules and narrower retinal arterioles [17]. A smaller study conducted by Garhöfer *et al.* (2004), performed on 12 male participants between 19 and 28 years old, concluded that retinal vessel diameter remained unchanged after glucose intake [21]. In addition, a study performed on 614 pregnant women by Li *et al.* (2016) in South-East Asia described the relationship between lower diet quality and wider retinal venules [18]. On the contrary, a cross-sectional study in the United Kingdom carried out by McEvoy *et al.* (2013), failed to find a relationship between three dietary patterns, called 'healthy', 'unhealthy' and 'snack and beverage' dietary patterns, and retinal vessel diameters [22].

Four studies have investigated the effect of macronutrient consumption. Among them, a large cross-sectional analysis in Australia found that higher consumption of carbohydrates was associated with arteriolar narrowing in girls and venular widening boys [23]. Meanwhile, a higher intake of fat and lower intake of protein was associated with wider retinal venular caliber in pregnant women [18]. Arteriolar narrowing and venular widening have also been described in relation to increased dietary Glycemic Index (GI) in cross-sectional analyses in children and in adults [23,24]. In the study of Sanchez-Aguadero *et al.* (2016), the association between GI and the retinal microvasculature in a cohort of 300 adults was examined [25]. The results indicated that a higher dietary GI implies a lowered Arterial-Venular Index (AVI), but failed to indicate associations for retinal vessel diameters [25]. Furthermore, high GI was associated with wider retinal venular caliber in the Blue Mountain Eye Study Cohort [24]. Moreover, the Maastricht Study showed that there was no relationship between dietary advanced glycation end products and CRAE or CRVE [26].

Four studies have reported that fiber intake is beneficial to retinal microvascular health. Kan *et al.* (2007) investigated the association between dietary fiber intake and retinal microvascular caliber in a cohort of adults in the Atherosclerosis Risk in Communities Study. According to the results of this study, dietary fiber intake was associated with wider retinal arteriolar caliber and narrower venular caliber [27]. Additionally, lower cereal fiber was associated with arteriolar narrowing and venular widening (Kaushik et al. 2009) and lower vegetable consumption (less than once a week) was associated with a decreased AVR (Dervenis et al. 2019) [24,28]. This is underlined by the finding that higher consumption of apples and pears (>150.1 g/day) is also associated with wider retinal arterioles and narrower retinal venules [29]. However, one randomized controlled trial described that there was no effect of increasing fruit and vegetable intake on the retinal vessel calibers [30].

Kumari *et al.* (2018), investigated the effect of the antioxidants lutein and zeaxanthin (carotenoids) on arteriolar and venular caliber, branching angle, fractal dimension and vascular tortuosity in an elderly population. The study reported that lower serum levels of both carotenoids were significantly associated with a narrower arteriolar caliber and wider venular caliber [31]. Contrastingly, higher intake of flavonoid subclasses proanthocyanin, anthocyanidin and isoflavone was associated with wider retinal arterioles and narrower retinal venules [29]. The same study also found that chocolate consumption (rich in the polyphenol epi-catechin) was inversely associated with retinal venular caliber. The latter finding is contradicted by a small randomized controlled trial in which there was no effect on CRAE, CRVE or AVI two hours after eating dark (polyphenol-rich) or white (polyphenol-free) chocolate in healthy individuals [32]. Other dietary antioxidants such as vitamin A and C, as well as elevated potassium intake, were associated with a narrower retinal venular caliber in adults [33]. On the contrary, vitamin B12 and folate were not significantly associated with a narrower retinal venular caliber. To date, only one study reported this result[34]. However, higher serum homocysteine (of which vitamin B12 and folate are metabolites) was associated with lower CRAE in men, but not women [34]. Another study conducted by Gopinath *et al.* (2020) concluded that higher dietary nitrate intake, specifically vegetable nitrate, was associated with wider retinal venules [35]. This same study also concluded that there was no significant effect on retinal caliber after non-vegetable nitrate intake. In a randomized controlled trial in Finland, intakes of alpha-tocopherol and beta-carotene were lower in smoking men who developed retinal vascular changes (including arteriolar narrowing) [36].

Higher consumption of dairy products, such as yogurt, cheese and milk has been linked to the beneficial retinal pattern of arteriolar widening and venular narrowing, while low consumption of dairy (less than 5 serves per week) has been linked to an opposite trend [37-39].

Furthermore, neither a low-salt nor a high-salt diet did affect the CRVE, CRAE and AVR in a randomized cross-over trial [40]. According to the study of Karatzi *et al.* (2016), red meat has a harmful effect on the microvasculature. The results suggested that red meat was inversely associated with CRAE [39].

Two studies highlighted the effect of fish and omega-3-fatty acid consumption on the retinal microvasculature [42,43]. Kaushik *et al.* (2008) reported that an increased consumption of oily fish was associated with both wider mean arteriolar and narrower venular diameter in adults [42]. Additionally, Gopinath *et al.* (2017) investigated the effect of fish consumption on retinal vascular caliber in children and adolescents. According to the results, increased fish consumption was primarily associated with widening of retinal arteriolar caliber in girls but not in boys [43].

Two studies were conducted on the effect of caffeinated drinks on the retinal microvasculature. Gin *et al.* (2023) reported that the acute effect of caffeinated drinks led to narrower retinal arteries and veins [44]. Karatzi *et al.* (2016) investigated the effect of caffeinated and alcoholic drinks on retinal vessel calibers in adults [41]. According to their results, consumption of decaffeinated and caffeinated coffee was associated with retinal vessel diameter [41]. Finally, a prospective cohort study from Rotterdam found that children who were never breastfed tended to have narrower retinal vessel calibers, particularly narrower venular calibers [19]. They also reported that breastfeeding duration and exclusivity and age at introduction of solid foods were not associated with retinal vessel calibers [19].

Looking at the differences in outcomes found related to different study types, associations between a healthy diet, wider retinal arterioles caliber and narrower retinal venules caliber were found in 14 studies of the in total seventeen cross-sectional analyses. 3 of the 5 cohort studies included found a positive relationship between diet and narrow retinal venules caliber and more wide retinal arterioles caliber.

Finally, six randomized-controlled studies were analysed of which one had a cross-over design. Only one RCT was able to find an association between retinal arteriolar narrowing and lower vitamin intake. The other five studies were not able to find any association. These studies all had a population size, ranging from 12-62 participants. The study of Teikari et al. which did find an association had a population size of 1072 participants.

Overall, the eligible papers have shown that several dietary components do affect the retinal microvasculature. Adherence to a healthy dietary pattern, high intake of dietary fiber, antioxidants, fish and dairy products have been shown to have beneficial effects on the microvasculature. Meanwhile, increased GI and red meat consumption have detrimental effects on the retinal microvasculature.

Smoking

More than half (n=15) of the included papers (n=25) on smoking were cross-sectional analyses. Six were prospective cohort studies, one was a retrospective cohort study, one was a non-randomized experimental trial, one study was a randomized controlled trial and one was a case-control study. Twelve studies were conducted in European countries, six were conducted in the USA, five were conducted in Asian countries, one was conducted in Australia and one was conducted in South Africa. The assessment of the quality of the studies resulted in good (n=4), fair (n=15) and poor (n=6). All studies on smoking behavior were performed on male and female adults aged older than 18 years. Two studies investigated the retinal microvasculature of children subject to maternal smoking during pregnancy. Moreover, there were two studies conducted on only male participants (Wimpissinger 2004, Resch 2005).

Most studies reported that both CRAE and CRVE were significantly larger in (habitual) smokers than in non-smokers [28,33,46-60]. Interestingly, six articles only describe the association between smoking and widening of CRVE and not widening of CRAE [33,47-50,53]. The African-PREDICT Study described that AVR and CRAE were also positively correlated with cotinine, the most prominent nicotine metabolite, in a group of individuals with low socio-economic status [53]. Inhalation of carbon monoxide (500 ppm) for 60 minutes, one of the major components of cigarettes, increased the diameter of retinal arteries and veins [46]. Those effects were not restricted to first hand smoking, as evidenced by the Hong Kong children eye study that suggested that children with second-hand smoke exposure are also affected by the effects of smoking. The Hong Kong Children eye study investigated the relationship between second-hand smoke exposure and retinal vascular parameters in a cohort of Chinese children aged 6 to 9 years old. According to this study, children who were exposed to second-hand smoking were more likely to have increased CRAE compared to children from smoke-free households [61]. In addition, two studies investigated the effect of maternal smoking during pregnancy [62,63]. The effects of maternal smoking during pregnancy on the retinal vessel caliber in childhood were investigated in the Generation R Study. The population-based study was conducted in a cohort of 3564 children aged between 5 and 8. According to the results, there was no association between smoking during pregnancy and adaptations in retinal vessel caliber in childhood [62]. In contradiction, a case-control study in Greece concluded that maternal smoking during pregnancy increased the frequency of Retinal Arteriolar Narrowing and Straightening (RANS) in neonates [63].

Nevertheless, four articles failed to find associations between smoking status and retinal microvessel diameters [45,64-66], and one article described an association between past and current smoking and focal arteriolar narrowing and general narrowing [67].

As mentioned, most of the included studies were cross-sectional analyses. 13 out of 15 (87%) included cross-sectional analyses concluded an association between (habitual) smoking and widened retinal arteriolar and venules. In comparison, 5 out of 8 (63%) included cohort studies found a correlation between these factors. Finally, one of the two randomized controlled trials draw a similar conclusion. Thus, findings between different study types were evident.

Overall, most included papers argue that smoking is associated with larger CRAE and CRVE. In addition, second-hand smoke exposure was associated with increased CRAE in children.

Physical Activity

In total, 28 studies contained an analysis on the effect of physical activity on the retinal microvasculature. Eight of those were cross-sectional analyses, nine others were trials, of which five had a cross-over design. Eight articles were prospective cohort studies, one was a case-control study, one was a retrospective cohort study, and one was a pre-post intervention study. Almost all studies (n=22) were conducted in European countries, four were conducted in the USA, one in Australia and one in Canada. The assessment of the quality of the studies resulted in good (n=5), fair (n=17) and poor (n=6). Most studies were conducted in both males and females aged 18 years and older. However, six studies included children and adolescents younger than 18 years old.

The most common finding in these studies was that individuals with higher level of physical activity had a healthier retinal microvascular pattern compared to sedentary controls [68-76]. The association was examined in the Atherosclerosis Risk in Communities (ARIC) Study in which 15792 males and females aged 45-64 years old were included. Physical activity levels were measured during leisure, sport and work. According to the results of this cross-sectional study, physical activity was associated with a lower prevalence of increased CRVE and indicated a preventive effect of physical activity of cardiovascular disease [69]. A cross-sectional study conducted by Anuradha *et al.* (2011) also found a correlation between low levels of physical activity and wider retinal venules [77].

Two studies investigated the effect of endurance exercise on the retinal microvasculature. Roeh *et al.* (2021) and Pressler *et al.* (2011) both investigated the effect of marathon running on retinal microvascularization in healthy individuals [72,73]. Roeh *et al.* (2021) found an increase in both CRAE and CRVE after marathon running, Pressler *et al.* (2011) found that marathon runners had significantly larger arterioles and smaller venules [72,73]. The effects of acute dynamic exercise of various intensities on retinal vessel diameter in adults were examined in the study of Nussbaumer *et al.* (2014). In alignment with previous studies on endurance exercise, they also reported an increase in CRAE and CRVE [78]. In addition, directly after extensive exercise, both retinal arterioles and venules were dilated [72,73,76,78-81]. Petersen *et al.* (2014) found that isometric exercise reduced contraction of retinal arterioles [82]. In contradiction, isometric exercise led to a decrease in retinal arterial and venular diameter [83-88]. Braun *et al.* (2018) concluded that higher VO_2 peak was associated with venular narrowing [89]. Furthermore, Hanssen *et al.* (2011) found that a high level of physical fitness was associated with an increased AVR [89]. In contrast to other findings, a prospective cohort-study held in seven European cities reported that there was no significant effect of physical activity on CRAE or CRVE [91].

Comparable to adults, retinal microvascular adaptations were associated with physical inactivity in children. Six studies were performed to examine the effect of physical activity and fitness in a population of children and adolescents [75,76,92-94]. Köchli *et al.* (2019), investigated the association between cardiovascular risk factors and CRVE in young children in the EXAMIN YOUTH study. They found that cardiorespiratory fitness was associated with wider CRAE and that slower sprint performance was associated with increased CRVE [94]. In line with those results, Imhof *et al.* (2016) also found that higher cardiorespiratory fitness measured by the 20m shuttle run test was associated with narrower CRVE and increased AVR in children [93]. A cohort study in Australia indicated that children who spent more time in outdoor sporting activities had wider mean retinal arteriolar caliber whereas those who spent more time watching television had narrower retinal arteriolar caliber [76]. Finally, a cluster randomized trial in children in Switzerland reported widening of retinal arteriolar diameters after implementation of a structured aerobic exercise program [92]. The same results were found in a randomized-controlled study from the Netherlands using only adults as participants where a widening of retinal arteriolar diameters was found. However, the study was not able to see changes in the retinal venules [95].

Overall, physical activity seems to be beneficial to retinal microvascular health. Isometric exercise led to a decrease in arteriolar and venular diameter, whereas endurance exercise induced an increase in retinal diameters. Furthermore, elevated cardiorespiratory fitness was associated with wider mean retinal arteriolar caliber in children. The results found in above mentioned studies are similar in almost all studies, regardless of study type.

Air Pollution

A total of 7 articles were included on the effect of air pollution on the retinal microvasculature. Six of those were prospective cohort studies and one was a cross-sectional analysis. Moreover, four of these studies were conducted in Belgium, one in the USA, one in Canada and one in South Africa. The assessment of the quality of the studies resulted in good (n=1) and fair (n=6). Six studies were conducted on both males and females, one study investigated the effect of air pollutants only in females [96].

The short- and long-term effect of $PM_{2.5}$ on the retinal microvasculature were investigated in the population-based Multi-Ethnic Study of Atherosclerosis (MESA). The results suggest that both short-term and long-term exposure to $PM_{2.5}$ are associated with a decrease in CRAE and an increase in CRVE in adults [97]. These findings were underlined by a cross-sectional study conducted in Belgium, which found arteriolar narrowing and venular widening in response to recent $PM_{2.5}$ exposure [98]. In the same study, chronic $PM_{2.5}$ exposure was shown to be related to wider retinal venules, but not to arteriolar diameter [98]. Another interesting finding of this study was that children living closer to major roads had smaller arteriolar diameters [98]. Meanwhile, a cross-sectional analysis in school children in Canada reported insignificant increases in CRAE associated with $PM_{2.5}$ exposures [99].

PM_{10} exposure was associated with a decrease in CRAE and CRVE in two studies conducted in Belgium [100,101]. Two studies investigated the effect of Black Carbon (BC) exposure. One study reported arteriolar and venular widening associated with short-term BC exposure [101], while the other observed venular widening associated with sub chronic BC exposure [102]. Furthermore, the effect of the gaseous air pollutant Nitrogen Dioxide (NO_2) on the retinal microvasculature in female South African populations was investigated in the study of Everson *et al.* (2019). The NO_2 levels in South Africa were lower compared to international standards of NO_2. Nonetheless, NO_2 was inversely associated with CRVE [96].

In conclusion, two studies suggest that $PM_{2.5}$ exposure is associated with a decrease in CRAE and an increase in CRVE. In addition, two studies report venular widening with BC exposure. Finally, one study presents that NO_2 exposure was inversely associated with CRVE.

Alcohol Consumption

The effect of alcohol on the retinal microvasculature was investigated in 9 articles. All of those nine were cross-sectional analyses. In addition, four studies were conducted in European countries, one in China, one in South Africa, one in the USA, one in Japan, and one was conducted in both the USA and Japan. The assessment of the quality of the studies resulted in good (n= 2) and fair (n=7). All studies were conducted on participants older than 18 years old and the majority included both males and females for analysis. One study was performed on only males between 35 and 59 years old [103].

The results of the included studies were conflicting. A large cross-sectional study in Japan concluded that habitual drinkers have higher CRVE and lower CRAE compared to nondrinkers [45]. The association between alcohol consumption and decreased retinal arteriolar diameter has also been described in four other studies [23,54,56,104]. Two of those were large cross-sectional studies, namely the Atherosclerosis Risk in Communities (ARIC) study in the USA and the Thessaloniki Eye Study in Greece. Both concluded that current alcohol drinkers have narrower arteriolar diameters compared to non-drinkers. In addition, a large cross-sectional study in South Africa suggested that in all socio-economic status groups (low and high) alcohol consumption is associated with decreased CRAE, and that in the high socio-economic status group, alcohol consumers had a lower AVR and wider CRVE compared to nondrinkers [54]. In contradiction, three studies reported no associations between alcohol consumption and retinal vessel diameters, however deriving their results from smaller study populations [41,49,103]. Another study, conducted in China, reported that alcohol consumption is correlated with generalized narrowing of retinal vessels [67].

All nine included studies were cross-sectional analyses. Thus, the outcomes of studies per study type cannot be compared to one another.

In summary, the results of the studies are contradictory. Although some studies report an association between alcohol consumption and decreased CRAE, several other studies did not find a relation between alcohol consumption and alterations in retinal vessel calibers.

Miscellaneous Environmental Exposures

In a cross-sectional analysis in 199 police officers from Buffalo, New York, the effect of shift work on the retinal microvasculature was studied. The police officers were predominantly male (145 male; 54 female) and the age ranged from 28 to 65 years old. Working night shifts was associated with significantly wider CRVE in former and current smokers. There were no significant associations with CRAE or in police officers who did not smoke [104].

The association between radiation and the retinal microvasculature in 1640 male and female atomic bomb survivors was investigated by Kiuchi *et al.* (2019). According to the results of this cross-sectional study, CRVE significantly decreases with increasing doses of radiation [105].

Discussion

This systematic review provides an overview of the effect of several dietary components, smoking, physical activity, air pollution, alcohol consumption and miscellaneous exposures on the retinal microvasculature in healthy individuals. The analysis was based on 86 studies representing the current state of research in this field.

Studies analyzing the effect of diet on the retinal microvasculature agreed that adherence to a healthy dietary pattern, high intake of dietary fiber, antioxidants, fish and dairy products are beneficial to the microvasculature. The eligible studies also suggest that adherence to unhealthy dietary patterns and high-GI diets are detrimental to microvascular health. However, these findings are largely based on cross-sectional associations. More randomized controlled intervention studies are needed to rigorously examine the cause-effect relationships between dietary components and retinal microvessel diameters.

Most studies indicated a positive association between smoking and retinal vessel diameter. This increase in both CRAE and CRVE might be explained by elevated Nitric Oxide (NO) production or potassium channel activation [59]. Furthermore, elastic tissue degeneration in smokers and smoking-related inflammation are proposed mechanisms of retinal vessel diameter increase [59,105]. However, several studies reporting positive association between smoking and CRVE did not find associations with CRAE. This indicates the need for more prospective cohort studies to investigate the effect of smoking on CRAE and CRVE separately. Studies also suggest that physical activity is beneficial to the retinal microvasculature. Isometric exercise was associated with a decrease in both arteriolar and venular diameter, meanwhile endurance exercise was associated with increased retinal microvascular diameters.

Most studies investigating the effect of $PM_{2.5}$ reported that both long- and short-term exposure to $PM_{2.5}$ was associated with a decrease in CRAE and CRVE. Finally, research evaluating alcohol consumption as a factor produced conflicting results, and no unanimous overview could be derived. Also, the assessment of alcohol consumption was heterogeneous between studies. Various studies categorized alcohol consumption as current, past and never [54-56], whereas Karatzi *et al.* distinguished between high alcoholic content drinks, wine and beer [41]. In addition, two other studies determined the absolute amount of alcohol consumed by participants, in grams or Japanese alcohol units [52,102]. These differences in assessment of alcohol consumption likely impede the formation of a cause-effect relationship with retinal microvascular diameters. Therefore, we recommend future studies to use either absolute amount of alcohol or the Japanese alcohol unit (1 unit= 22.9g alcohol) when investigating the effect of alcohol consumption on the retinal microvasculature.

The associations we report are in line with the previous knowledge reviewed by Serre *et al.* (2012) [6]. Both reviews comparably report the beneficial patterns associated with higher intake of dietary fiber and fish consumption, as well as the harmful effect of high-GI diets on the retinal microvasculature. While both reviews report the unfavorable effects of sedentary behavior and the favorable effects of higher levels of physical activity, we hereby include outcomes specific to exercise types, such as isometric or endurance exercise. Both reviews highlight the association between cigarette smoking and wider retinal vessel calibers. Furthermore, the results on air pollution reviewed hereby are concur with Serre *et al.* (2012) [6]. Our review distinctively included findings related to alcohol consumption, exercise type and miscellaneous exposures. Specifically, the present review presents new insights into the effects of shift work, television viewing time and radiation on the retinal microvasculature.

The conclusion drawn in our review about the effects of physical activity and sedentary behavior is also underlined by the review of Sousa-Sá *et al.* (2020) [11]. Finally, the findings presented in our review, regarding dietary influence on the retinal microvasculature, are in accordance with Keel *et al.* (2016) [12].

Overall, the influence of the environment on microvasculature can be beneficial or deleterious. A healthy diet pattern and regular physical activity stimulates the health of microvasculature, while smoking, consumption of alcohol and air pollution are detrimental to microvessels and increase CVD risk. Understanding these effects on microvascular health can support the development of preventive healthcare oriented towards cardiovascular health. This could be implemented into lifestyle coaching, health education or policy development aiming at improving public health [106].

This systematic review identified a number of limitations of the current published papers investigating the effect of environmental exposures on the microvasculature. Firstly, five of the included observational studies were at high risk of bias or displayed some concerns. However, the contribution of these observational studies was minor considering the total amount of observational studies included in the review. As for the included experimental studies, two studies were considered to present high risk of bias. The low score seemed to be derived from the fact that the method of randomization was inadequate and an incorrect use of intention to treat analysis.

Secondly, most of the included studies are cross-sectional analyses. To obtain potential causal relations between environmental exposures and the retinal microvasculature, more randomized controlled intervention studies are needed, and if not possible due to ethical considerations, more prospective cohort studies should investigate the effect on the retinal microvasculature. Thirdly, the characteristics of the study populations and control groups differed between the included studies. This could explain the conflicting results on alcohol consumption. In addition, sample size differed vastly between included studies. Furthermore, the majority of the studies is conducted in the countries in North America, Europe and Australia, especially in European countries. For instance, all studies on the effect of physical activity were performed in North America, Europe and Australia. Although these studies give valuable associations in European populations, the results might not apply to other populations. Ideally, studies performed in South American, African and Asian countries would give insights whether the same associations hold true in other populations.

In conclusion, our review presents a comprehensive overview of the current literature on the effect of environmental exposures on the retinal microvasculature. For dietary factors and air pollution, the investigated parameters demonstrated consistent outcomes. Future studies focusing on dietary factors would benefit from investigating micronutrient and individual dietary products, in addition to dietary patterns and macronutrients. Additional research on air pollution should focus on the effects of $PM_{2.5}$, PM_{10}, black carbon and Nitrogen Dioxide (NO_2), which were scarcely investigated. Furthermore, other forms of air pollution (e.g. carbon monoxide, lead and sulphur dioxide) should also be included in future research. Overall, the effect of cigarette smoking was denoted by an increase in CRVE and CRAE, with a varying effect on CRAE between studies. To establish a more robust causal link between smoking and changes in retinal microvessel calibers, future research quantifying cigarette smoking is necessary, merely comparing smoking status categories produces inconsistent results. Similarly, the effect of alcohol consumption on retinal microvessel calibers is unclear.

Quantifying the absolute alcohol consumption in participants may produce more consistent results and enable the elucidation of a cause-effect relationship. Improving scientific understanding of these effects on microvascular health can support the development of preventive healthcare and public health policies oriented towards cardiovascular health.

Author Statements

Author Contributions

Stan Zuidervaart: Investigation, Data Curation, Writing- Original Draft, Visualization; Anne Gielen: Investigation, Data Curation, Writing- Review & Editing, Visualization; Jesper van Os: Investigation, Data Curation, Writing- Review & Editing, Visualization; Jarod Simonet: Investigation, Data Curation, Writing- Review & Editing, Visualization; Luna Ali: Investigation, Data Curation, Writing- Review & Editing, Visualization; Karlijn de la Rambelje: Investigation, Data Curation, Writing- Original Draft, Visualization; Simone van Breda: Conceptualization, Writing- Review & Editing, Supervision.

Disclosure of Competing Interest

The authors declare to have no competing interest.

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