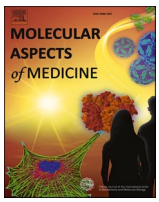
Molecular Aspects of Medicine 93 (2023) 101203

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam



Review

Towards modifying the genetic predisposition for glaucoma: An overview of the contribution and interaction of genetic and environmental factors

Kelsey V. Stuart [a], Louis R. Pasquale [b], Jae H. Kang [c], Paul J. Foster [a], Anthony P. Khawaja [a,*]

[a] NIHR Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK
[b] Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[c] Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Keywords:
Glaucoma
Risk factors
Genetics
Gene-environment interactions
Review

ABSTRACT

Glaucoma, the leading cause of irreversible blindness worldwide, is a complex human disease, with both genetic and environmental determinants. The availability of large-scale, population-based cohorts and biobanks, combining genotyping and detailed phenotyping, has greatly accelerated research into the aetiology of glaucoma in recent years. Hypothesis-free genome-wide association studies have furthered our understanding of the complex genetic architecture underpinning the disease, while epidemiological studies have provided advances in the identification and characterisation of environmental risk factors. It is increasingly recognised that the combined effects of genetic and environmental factors may confer a disease risk that reflects a departure from the simple additive effect of the two. These gene-environment interactions have been implicated in a host of complex human diseases, including glaucoma, and have several important diagnostic and therapeutic implications for future clinical practice. Importantly, the ability to modify the risk associated with a particular genetic makeup promises to lead to personalised recommendations for glaucoma prevention, as well as novel treatment approaches in years to come. Here we provide an overview of genetic and environmental risk factors for glaucoma, as well as reviewing the evidence and discussing the implications of gene-environment interactions for the disease.

1. Introduction

Glaucoma comprises a heterogeneous group of disorders characterised by chronic progressive optic neuropathy and corresponding stereotypical visual field changes. The final common pathway for all forms of the disease is marked by retinal ganglion cell (RGC) degeneration and optic nerve fibre loss. Glaucoma is the leading cause of irreversible blindness worldwide, currently estimated to affect 76 million individuals aged 40–80 years, with projections rising to 112 million by 2040 (Tham et al., 2014). Globally, 2.1 million individuals are blind, and a further 4.2 million visually-impaired, as a result of the disease (Bourne et al., 2016).

Despite extensive research, the precise pathophysiological mechanisms underlying glaucomatous neurodegeneration remain unclear, although numerous hypotheses have been proposed (Stein et al., 2021). The biomechanical and vascular theories implicate intraocular pressure (IOP)-mediated mechanical stress and optic nerve head (ONH) vascular insufficiency, respectively, while a third theory posits a primary neurodegenerative component to the disease, especially when glaucomatous changes occur in the absence of raised IOP (normal tension glaucoma, NTG).

Glaucoma can be broadly categorised into two groups – open-angle glaucoma and angle-closure glaucoma – based on the configuration of the anterior chamber drainage angle. Both subtypes can occur as primary disease (>90% of cases) or secondary to an identifiable underlying mechanism (Quigley, 1996). In primary open-angle glaucoma (POAG) there is a normal anatomical drainage angle and no identifiable secondary cause for glaucoma (e.g., ocular pigment, exfoliation material, or inflammatory debris). POAG accounts for >80% of all glaucoma cases worldwide and is a highly complex disease, with both genetic and environmental determinants (Stein et al., 2021).

Well-established non-modifiable risk factors for POAG include older age, non-White ethnicity, and family history of glaucoma (Stein et al., 2021) – with the last two almost certainly reflecting some degree of genetic influence. Similarly, elevated IOP, the only known modifiable risk factor for glaucoma, is a heritable trait, with considerable overlap in

* Corresponding author. UCL Institute of Ophthalmology, 11–43 Bath Street, London, EC1V 9EL, UK.
E-mail address: anthony.khawaja@ucl.ac.uk (A.P. Khawaja).

https://doi.org/10.1016/j.mam.2023.101203
Received 30 March 2023; Received in revised form 26 June 2023; Accepted 5 July 2023
Available online 8 July 2023

the underlying genetic architecture of IOP and glaucoma (Khawaja et al., 2018). Numerous landmark interventional studies have proven the clinical benefit of lowering IOP on reducing the risk for the onset or progression of disease (Kass et al., 2002; Heijl et al., 2002), and this beneficial effect has also been demonstrated for NTG (Collaborative Normal-Tension Glaucoma Study Group, 1998), in which baseline IOP is within the normative population range, even before intervention. It is hypothesised that certain factors, including vascular dysregulation and abnormal pressure gradients across the lamina cribrosa, may render individuals with NTG more susceptible to IOP-mediated mechanical stress, resulting in glaucomatous damage at seemingly normal pressures (Killer and Pircher, 2018). Although all currently approved glaucoma interventions (including medication, laser, and surgery) work by lowering IOP, there is considerable interest in identifying other modifiable risk factors, which may complement existing treatment strategies or guide lifestyle recommendations.

2. Glaucoma genetics

Glaucoma is one of the most heritable of all complex human diseases (estimated h^2, 0.70) (Wang et al., 2017), with first-degree relatives of individuals with glaucoma having an almost 10-fold greater lifetime risk of disease compared to the general population (Wolfs et al., 1998). In the paediatric setting, monogenetic mutations associated with primary congenital glaucoma are the most common cause of disease, accounting for a significant proportion of all childhood blindness (Lewis et al., 2017). Conversely, only a small proportion of POAG in adults (estimated to be <5%) is inherited in a Mendelian fashion (Stein et al., 2021). *MYOC* (myocilin) gene sequence variations give rise to the most common form, characterised by elevated IOP; while rare missense mutations in *OPTN* (optineurin) and copy number variations involving *TBK*-1 (TANK-binding protein 1) can cause familial NTG (Sears et al., 2019). These highly penetrant autosomal-dominant genetic mutations tend to have large biological effects, causing clinically severe early-onset disease (Wiggs and Pasquale, 2017). In this small subset of individuals, genetic testing of unaffected relatives may guide screening strategies, with a *MYOC* cascade genetic testing approach shown to identify at-risk individuals at a significantly younger age and with less severe disease than those presenting through traditional clinical referral pathways (Souzeau et al., 2017). Advances in genome-editing technology also holds the promise of curative precision medicine for these patients in the future. Disruption of mutant *MYOC* and its function using CRISPR-Cas9 resulted in lower IOP and prevented further glaucomatous damage in a mouse model of the disease (Jain et al., 2017a).

The genetics underpinning the vast majority of adult-onset POAG, however, is far more complex. In these cases, a multitude of genetic factors, each relatively common but of small individual effect, cumulatively contribute towards the risk of disease. In the last decade, hypothesis-free genome-wide association studies (GWAS) have driven the discovery of these common genetic determinants of glaucoma, with more than 100 POAG susceptibility loci reported to date (Choquet et al., 2020; Gharahkhani et al., 2021). This line of research has been greatly accelerated by the emergence of large-scale biobank-based cohorts and collaborative genetic consortia, the widespread availability of GWAS summary statistics to the scientific community, and advances in post-GWAS genetic analyses (Choquet et al., 2020). Despite this rapid progress, current knowledge of genome-wide significant ($P < 5 \times 10^{-8}$) single nucleotide polymorphisms (SNPs) explains less than 10% of the genetic contribution to POAG susceptibility, suggesting that additional variants are yet to be discovered (Craig et al., 2020).

To aid genetic discovery, the definitive case-control GWAS approach has been supplemented by the examination of heritable quantitative traits – termed endophenotypes – related to glaucoma. This approach, which includes analysis of IOP and optic disc parameters, is not reliant only on data from disease cases, but can instead leverage data from a healthy population by assessing the variation of an endophenotype across a spectrum of health and disease. In this way, population cohorts can contribute to analyses, greatly increasing sample size and power to detect small associations. Statistical power is also increased by analysing continuous traits rather than binary outcomes. Using this approach, more than 100 genetic loci associated with both IOP (Khawaja et al., 2018; Choquet et al., 2017), the cardinal modifiable risk factor for glaucoma, and vertical cup-disc ratio (Han et al., 2021), a marker of glaucomatous ONH damage, have been identified. Results from these analyses have shed light on the underlying pathophysiology of glaucoma (Choquet et al., 2020), while meta-analysis of this genetic data, using a multitrait approach, has further enabled POAG genetic discovery (Craig et al., 2020).

3. Polygenic risk scores

Although each SNP identified through GWAS explains only a small proportion of heritability and is generally insufficient to cause disease, the additive effects of multiple common variants across the genome can confer a genetic risk equivalent to that seen in monogenic disease (Khera et al., 2018). This cumulative genetic burden can be distilled into a single probabilistic value – a polygenic risk score (PRS) – that represents a quantitative summary of an individual's genetic susceptibility to a specific trait or disease (Qassim et al., 2021). At its most basic, an unweighted PRS is a simple sum of the number of risk variants carried by an individual. More commonly, however, the variants are weighted by their magnitude of effect (based on the GWAS results), allowing for better risk prediction by accounting for both the total number of variants and the individual variant effect sizes (Chatterjee et al., 2016). In a clinical context, the utility of a PRS is not as a diagnostic tool, but rather as a means of disease risk stratification, allowing for categorisation of individuals according to their level of underlying genetic risk. Those identified to be at high risk of disease (with a PRS in the top 20% of the normal population or study cohort, for example) may then benefit from modified screening approaches or targeted interventions (Qassim et al., 2021). The clinical utility of PRS has already been reported in a host of complex non-communicable diseases, including cardiovascular disease, diabetes, and cancer (Torkamani et al., 2018).

Given the high heritability of POAG, as well as the clinical effectiveness of early interventions in preventing otherwise irreversible vision loss, the application of PRS to glaucoma risk stratification has been a research focus in recent years (Qassim et al., 2021). Early studies, generally based on a restricted set of genetic variants and applied to relatively small cohorts, were only able to demonstrate modest discriminatory powers, with limited clinical potential (Mabuchi et al., 2017; Tham et al., 2015; Zanon-Moreno et al., 2017). Backed by larger GWAS, however, recent work has been able to demonstrate risk stratification and predictive ability with clear potential for translational benefit. For example, a glaucoma PRS based on 146 IOP-associated SNPs was found to be associated with higher IOP, younger age of glaucoma diagnosis, more family members affected, and higher treatment intensity in an independent cohort (Qassim et al., 2020). More recently, a comprehensive POAG PRS, based on 2673 uncorrelated genetic variants identified using a multitrait approach, demonstrated even greater risk stratification in an independent cohort, with those in the top decile of the PRS distribution having an almost 15-fold greater risk for glaucoma relative to those in the bottom decile (Craig et al., 2020). The same PRS was also found to predict disease progression in early manifest glaucoma cases and surgical intervention in advanced disease (Craig et al., 2020; Siggs et al., 2022). Although not intended as diagnostic tools, regression-based POAG risk prediction models based on recent PRS can now achieve an area under the receiver operating characteristic curve (AUC) of 0.76,[5,19] considered an "acceptable" level of discriminatory power for a diagnostic test (Mandrekar, 2010).

4. Environmental risk factors

While genetic susceptibility undoubtedly contributes a substantial proportion to individual risk, glaucoma is a complex disease and environmental determinants also play a role. Given recent advances in glaucoma PRS development, it may soon be possible to identify individuals at high risk of glaucoma before they exhibit any signs of disease, making the identification of environmental factors that could potentially modify genetic risk a particular priority.

Some factors, such as playing high-resistance wind instruments, ingesting caffeine, certain yoga positions, wearing tight neckties, and lifting weights are known to increase IOP; while others, including general physical activity and consuming alcohol, lower IOP (Pasquale and Kang, 2009). However, it is unclear whether these short-term changes are sufficient to meaningfully impact glaucoma risk, and the overall effect of habitual behaviours are less clear. Certain factors may also influence glaucoma risk through IOP-independent mechanisms by affecting the rate of RGC apoptosis (Wiggs, 2012) – various dietary factors, including antioxidants and essential fatty acids, have been implicated as potentially neuroprotective in glaucoma (Kumar and Agarwal, 2007; Al Owaifeer and Al Taisan, 2018), while others, notably alcohol, are known to be neurotoxic (Stuart et al., 2022a). A further consideration is the potential for "environmental antagonistic pleiotropism" – in which an environmental exposure may simultaneously generate biological responses that offset one another (Pasquale and Kang, 2009). However, despite extensive research and numerous reported associations, no single environmental factor has been proven as an interventional target for glaucoma in clinical trials. A brief review of the role of common environmental factors in glaucoma follows.

Alcohol: The short-term effects of alcohol ingestion include a transient, dose-dependent reduction in IOP (Buckingham and Young, 1986; Harris et al., 1996; Houle and Grant, 1967; Giurlani et al., 1978; Luksch et al., 2009; Peczon and Grant, 1965; Weber et al., 2013; Yamada et al., 1995) and an increase in ONH blood flow (Weber et al., 2013; Kojima et al., 2000), theoretically playing a protective role in the development of glaucoma. The effects of habitual alcohol consumption on IOP and glaucoma, however, are less clear, with several population-based studies reporting an adverse association between alcohol use and IOP (Leske et al., 1996; Lin et al., 2005; Song et al., 2020; Wu et al., 1997; Yoshida et al., 2003; Stuart et al., 2022b), although this is not always a consistent finding (Seddon et al., 1983; Weih et al., 2001). Very few studies have been designed specifically to assess the relationship between alcohol consumption and glaucoma, and while adverse associations have been reported (Stuart et al., 2022b; Wise et al., 2011), most observational studies have yielded null results (Leske et al., 1996, 2001; Bikbov et al., 2020; Bonomi et al., 2000; Charliat et al., 1994; Chiam et al., 2018; Renard et al., 2013; Jiang et al., 2012; Kang et al., 2007; Pan et al., 2017). Systematic review and meta-analysis of these studies suggests that habitual alcohol consumption is adversely related to both IOP and glaucoma, although the quality of evidence is low (Stuart et al., 2022a). Alcohol intake does appear to be consistently associated with a thinner inner retina (Stuart et al., 2022b; Khawaja et al., 2020; Lamparter et al., 2018; Paulsen et al., 2021; Han et al., 2020) – a structural characteristic of glaucoma (Kim and Park, 2018; Oddone et al., 2016) – with recent Mendelian randomisation (MR) experiments suggesting a causal relationship (Stuart et al., 2022b).

Smoking: Exposure to harmful compounds found in tobacco smoke has been postulated to be a risk factor for glaucoma through ischaemic or oxidative mechanisms (Jain et al., 2017b). Conversely, nicotine has been hypothesised to be a protective factor through nitric oxide-induced vasodilatory properties (Toda and Nakanishi-Toda, 2007). While acute exposure has been shown to have detrimental effects on the ocular surface and tear function (Latif and Naroo, 2022), there appears to be little short-term effect on IOP or ONH perfusion (Tamaki et al., 2000). Despite these experimental results, multiple population-based studies have reported higher IOP in smokers compared to non-smokers (Lee et al., 2003; Yoshida et al., 2014; Lee et al.), with findings from the UK Biobank suggesting that this may be related to altered corneal biomechanical properties rather than a true ocular hypertensive effect (Chan et al., 2016). The evidence for the role of smoking in glaucoma is conflicting and inconclusive. Most studies have reported null (Wise et al., 2011; Charliat et al., 1994; Juronen et al., 2000; Kang et al., 2003; Klein et al., 1993; Quigley et al., 1994; Ramdas et al., 2011; Wang et al., 2012; Wilson et al., 1987) or adverse (Renard et al., 2013; Fan et al., 2004; Kaimbo et al., 2001; Katz and Sommer, 1988; Le et al., 2003) associations, especially in current or heavy smokers (Jain et al., 2017b), but there is also evidence suggesting a potentially protective association (Buys et al., 2012; Founti et al., 2020; Doshi et al., 2008; Tran et al., 2023), despite an uncertain explanatory mechanism.

Caffeine: Numerous studies have examined the effect of caffeine-containing products (which include coffee, tea, carbonated drinks, and chocolate products) on ocular parameters of both healthy participants (Vera et al., 2019; Redondo et al., 2020; Terai et al., 2012; Dervişoğulları et al., 2016; Ozkan et al., 2008; Okuno et al., 2002; Ajayi and Ukwade, 2001; Lotfi and Grunwald, 1991; Okimi et al., 1991; Adams and Brubaker, 1990) and glaucoma patients (Jiwani et al., 2012; Avisar et al., 2002; Tran et al., 2014; Higginbotham et al., 1989), with most demonstrating a modest short-term elevation in IOP and reduction in ONH blood flow. Although this ocular hypertensive effect does not translate to epidemiological studies of habitual caffeine use in the general population, there does appear to be an adverse association with IOP in individuals with, or at high genetic risk for, glaucoma (Chandrasekaran et al., 2005; Kim et al., 2021). Similarly, while studies of the association between caffeine and glaucoma have reported conflicting results (Kim et al., 2021; Wu et al., 2018; Kang et al., 2008; Pasquale et al., 2012; Bae et al., 2020), an adverse relationship may only be apparent in individuals with a high genetic susceptibility to glaucoma (Kim et al., 2021; Kang et al., 2008; Pasquale et al., 2012). Recent MR experiments have provided further evidence that habitual caffeine consumption may be causally related to an increased risk for POAG (Li et al., 2022).

Physical activity: Bouts of physical activity are well documented to cause a transient reduction in IOP in both healthy individuals (Yan et al., 2016; Read and Collins, 2011; Avunduk et al., 1999; Ashkenazi et al., 1992; Martin et al., 1999; Natsis et al., 2009; Leighton and Phillips, 1970; Harris et al., 1994; Conte et al., 2014; Price et al., 2003; Qureshi, 1995) and glaucoma patients (Natsis et al., 2009; Qureshi, 1995), as well as an increase in ocular blood flow and perfusion of the ONH and retina (Price et al., 2003; Vo Kim et al., 2019; Alnawaiseh et al., 2017; Li et al., 2021). Fewer studies have assessed the association of habitual physical activity with IOP (Qureshi et al., 1996; Fujiwara et al., 2019) and glaucoma (Wang et al., 2019; Williams, 2009; Meier et al., 2018; Lin et al., 2017). While protective associations have been reported for both greater levels of physical activity and greater cardiovascular fitness (Qureshi et al., 1996; Fujiwara et al., 2019; Williams, 2009; Meier et al., 2018), this is not always a consistent finding in epidemiological studies (Wang et al., 2019; Lin et al., 2017; Madjedi et al., 2023).

Diet: There is considerable interest in the role that diet may play in modulating glaucoma risk and various individual dietary components have been studied in relation to the disease (Pasquale and Kang, 2009; Al Owaifeer and Al Taisan, 2018). Studies suggest that oxidative stress may play a role in glaucoma (Kumar and Agarwal, 2007), and many dietary factors are hypothesised to be neuroprotective through antioxidative mechanisms. These include *Ginkgo biloba* extract (which may also increase ocular blood flow and be of particular importance in NTG) (Chung et al., 1999; Hirooka et al., 2004; Eckert et al., 2005; Park et al., 2011; Shim et al., 2012; Quaranta et al., 2003; Lee et al., 2013), flavonoids (a polyphenol compound commonly found in green tea, red wine, and cocoa) (Patel et al., 2015; Kang et al., 2018), fruits and vegetables (nitrate-rich green leafy vegetables, in particular, are further hypothesised to play a role through nitric oxide signalling) (Coleman et al., 2008; Giaconi et al., 2012; Kang et al., 2016). Despite these findings, the

use of antioxidant supplementation has not consistently shown a beneficial association with glaucoma (Wang et al., 2013; Garcia-Medina et al., 2015; Moreno-Montañés et al., 2022). There is also evidence that dietary niacin (vitamin B3) may be protective in glaucoma, potentially through favourable effects on neural tissue and mitochondrial function (Hui et al., 2020; Taechameekietichai et al., 2021). Dietary factors implicated as potentially harmful in glaucoma include essential fatty acids (specifically an omega-3:omega-6 imbalance) (Ren et al., 2006; Pérez de Arcelus et al., 2014; Kang et al., 2004), and excessive sodium intake (Tseng et al., 2022). Although low-carbohydrate dietary patterns, theorised to enhance mitochondrial function and have antioxidant effects (Miller et al., 2018), were not consistently associated with glaucoma in three large US prospective studies (Hanyuda et al., 2020), a combined Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diet, which incorporates various individual dietary components discussed above, was recently associated with a lower risk for incident glaucoma in the Rotterdam Study (Vergroesen et al., 2023).

Stress: The complex systemic response associated with emotional and psychological stress has been postulated to play a role in glaucoma through various pathogenic mechanisms induced by chronic elevation and non-physiological patterns of cortisol release (Russell and Lightman, 2019). While acute stress has been shown to elevate IOP (Brody et al., 1999; Méndez-Ulrich et al., 2018; Gillmann et al., 2019; Abe et al., 2020; Kaluza et al., 1996), chronic stress and anxiety have recently been reported to be adversely associated with glaucoma (Shin et al., 2021; Berchuck et al., 2021). Stress-reduction strategies, including pharmacological and meditation-based approaches, have been shown to have beneficial effects on both IOP (Ismail and Mowafi, 2009; Dada et al., 2018, 2022) and ONH perfusion (Dada et al., 2021).

Air pollution: Ambient air pollution (from sources including coal combustion, automotive vehicle emissions, and biofuels) is recognised as an important contributor to the global disease burden and has been hypothesised to affect glaucoma through neurotoxic or vascular mechanisms (Cohen et al., 2017; Grant et al., 2022). Exposure to particulate matter less than 2.5 μm in diameter ($PM_{2.5}$) has consistently been linked to a higher prevalence of glaucoma in epidemiological studies (Chua et al., 2019; Sun et al., 2021; Grant et al., 2021; Yang et al., 2021), with no evidence for an adverse association with other forms of air pollution (Grant et al., 2022).

In addition to environmental exposures, various medical conditions (Stein et al., 2021), metabolic risk factors (Roddy, 2020) and systemic medications (Wu et al., 2020) have been associated with glaucoma. A detailed overview of these relationships is beyond the scope of this review and the reader is directed to the relevant references for further information. Given the complexity of glaucoma, it is likely that these factors modulate disease risk in a similar manner to genetic factors – while the effect of individual factors may be small and generally insufficient to cause disease, the cumulative contribution of multiple factors may prove to confer appreciable risk. Although strong evidence is lacking, in general, recommendations for modifiable interventions in glaucoma can be aligned with those for overall health – appropriate management of comorbid health conditions, maintaining a normal metabolic profile, avoiding known occupational hazards, regular physical activity, a healthy diet, and effective stress management.

5. Gene-environment interactions

While both genetic and environmental factors can independently influence glaucoma risk, a further aetiological consideration is the interplay between the two. Studies of gene-environment interaction aim to describe how genetic and environmental factors jointly influence disease risk (Hunter, 2005). Importantly, the combined effect of gene and environment may confer a risk that reflects a departure from the simple additive effect of the two. For example, an environmental exposure may only cause an effect or be associated with a disease in the presence of a certain genetic variant (e.g., the alcohol-induced flushing response seen in individuals with low-activity polymorphisms in the *ALDH2* (aldehyde dehydrogenase 2) gene) (Edenberg, 2007). Alternatively stated, the risk of disease associated with a particular genotype may be modified by changing the level of exposure to an environmental risk factor (e.g., the risk of developing emphysema in individuals with alpha-1 antitrypsin deficiency caused by *SERPINA1* (serpin family A1) mutations can be modified by altering exposure to cigarette smoke). (Lockett et al., 2012).

Better characterisation of gene-environment interactions has several possible benefits, including offering insights into underlying biological pathways, allowing for improved public health policy through targeted population screening, and filling the missing heritability gap for complex traits (Hunter, 2005). However, despite considerable interest, studies of gene-environment interaction have historically been limited by a lack of adequately powered studies with the necessary genetic and environmental data to perform these analyses (Manolio et al., 2006). This challenge has been partially overcome by the advent of large-scale, population-based, prospective cohort studies, such as the UK Biobank (Sudlow et al., 2015; Bycroft et al., 2018), which have revolutionised epidemiological research in recent decades (Manolio et al., 2020). The increasing availability of large cohorts with detailed ophthalmic, genetic, and environmental data has allowed for greater consideration to be given to gene-environment interactions in glaucoma.

An early research focus was the role of the *NOS3* (nitric oxide synthase 3) gene in mediating glaucoma risk. The NOS3 enzyme catalyses the production of nitric oxide, which in turn influences luminal smooth muscle tone (Pollock et al., 1991). This isoform is present in the human outflow pathway and the endothelial cells of the RGC vasculature (Nathanson and McKee, 1995; Garthwaite et al., 2006), making it of interest in glaucoma. In a nested case-control study of the Nurses' Health Study and Health Professionals Follow-up Study, while no *NOS3* polymorphism was associated with POAG overall, a significant interaction was observed between various *NOS3* SNPs and post-menopausal hormone (PMH) use in women (Kang et al., 2010). Although PMH use has previously been implicated as a protective factor in glaucoma (Madjedi et al., 2022), these findings suggest that sex-based biology and reproductive hormones may play a role in POAG pathogenesis and offer insights into potential underlying disease mechanisms. In a similar analysis, the associations of hypertension and cigarette smoking with POAG risk were also found to depend on *NOS3* genetic polymorphisms (Kang et al., 2011), again suggesting that nitric oxide signalling may play an important role in mediating the effect of environmental risk factors on glaucoma risk.

While these studies examined environmental interaction with a single genetic locus, recent advances in PRS development have now made it possible to assess the interaction between an environmental factor and the cumulative effect of multiple genetic variants. For example, it has been shown that for women in the highest decile of non-modifiable risk for breast cancer (based in part on a 92-SNP breast cancer PRS), their absolute lifetime risk could be reduced to an average level by modifying body mass index, PMH use, alcohol intake and smoking (Maas et al., 2016). Although this approach may not yield specific insights into underlying biological pathways, it may have important implications for targeted population screening and personalised recommendations for primary preventative measures.

Recently, the same approach has been applied to the study of glaucoma-related gene-environment interactions. In a study of more than 100,000 UK Biobank participants, caffeine consumption was found to be associated with both higher IOP and glaucoma prevalence, but only in those at the highest genetic susceptibility to higher IOP (based on a 111-SNP IOP PRS) (Khawaja et al., 2018; Kim et al., 2021). Specifically, among those with a PRS in the top 25% of the study population, consuming >480 mg/day versus <80 mg/day of caffeine was associated with a 0.35-mmHg higher IOP (Kim et al., 2021). Although this population-level difference may appear small, it is equivalent in magnitude to the effect of *TMCO1* rs10918274, the gene variant with the

strongest effect on both higher IOP and POAG risk (Khawaja et al., 2018).

In a similar UK Biobank analysis, alcohol consumption was demonstrated to be adversely associated with IOP, but again only in those with the greatest genetic risk for glaucoma (based on the previously described 2673-SNP multitrait glaucoma PRS) (Craig et al., 2020; Stuart et al., 2022b). While no association between alcohol intake and IOP was observed in those with a PRS in the bottom 20% of the distribution, progressively stronger associations were noted in those at higher genetic risk, with those in the top 20% having 0.15-mmHg higher IOP per standard deviation greater weekly alcohol intake (Stuart et al., 2022b). Together, these results provide preliminary evidence that individuals with a high genetic susceptibility to glaucoma may be able to meaningfully reduce their absolute risk of disease by modifying their exposure to two common dietary factors.

6. Discussion

Until recently, technical and financial considerations have largely restricted complex disease genetics and PRS application to the realm of scientific research; however, rapid advances in the field have now placed these firmly in the public domain. Many commercial enterprises (e.g., 23andMe, www.23andme.com) now offer publicly-accessible genotyping services and provide a range of personalised health insights – including PRS calculation – based on an individual's genetic data. Ambitious projects, such as Our Future Health (www.ourfuturehealth.org.uk) which aims to genotype 5 million UK adults by 2025, provide further indication that population-scale genotyping is fast becoming a distinct reality. As we approach a future where individual genetic data and polygenic risk are readily available, knowledge of gene-environment interactions will become increasingly relevant to the management of glaucoma and has two important fundamental implications:

Primary prevention: While the onset of POAG typically occurs from middle-age onwards, any underlying genetic predisposition to the disease is fixed from birth. Applied to a sufficiently young population, a PRS could identify those individuals at high risk for developing glaucoma, but before the overt onset of disease. While these individuals may benefit from targeted screening and regular ophthalmic examinations (population-level screening for glaucoma is currently not recommended (Stein et al., 2021)), it also raises the possibility of primary disease prevention – high-risk individuals could delay, and potentially prevent, the onset of disease by modifying environmental exposures. Genetic risk stratification with subsequent environmental modification, including physical activity and statin therapy, in disease-free individuals has already been suggested as a primary preventative measure for coronary artery disease (Roberts et al., 2021). This paradigm shift in complex disease management has the potential to revolutionise preventative medicine in the future.

Personalised medicine: As knowledge of gene-environment interactions in glaucoma improves, so will the ability to provide individualised glaucoma management. In future, genetic profiles could guide targeted environmental recommendations, allowing high-risk individuals to modify their absolute disease risk and providing them greater autonomy in the management of their health. This personalised approach may also aid a physician's glaucoma management plan. Genetic data may guide optimal therapeutic choices (e.g., by predicting which individuals will respond to particular ocular hypotensive medication classes or laser therapy) and could lead to improved clinical outcomes and more efficient use of limited healthcare resources. The use of pharmacogenetics to guide treatment options has recently been advised for several common medications, including opioids and antidepressants, in the UK (Mahase, 2022), and it is not implausible that this approach may eventually prove to become common practice when prescribing glaucoma therapeutics in future.

Further discovery of glaucoma-associated genetic variants and environmental risk factors, coupled with ongoing advances in analytical tools to explore gene-environment interactions (Westerman et al., 2021), promise to greatly improve our understanding of this complex disease and enable novel disease management strategies in years to come.

Financial support

KVS: UCL Overseas Research Scholarship, Fight for Sight (London) (1956A) and The Desmond Foundation. LRP: NEI EY015473, NEI EY032559, The Glaucoma Foundation (NYC), Challenge Grant from Research to Prevent Blindness (NYC). PJF: Alcon, Fight for Sight (London) (1956A) and The Desmond Foundation. APK: UK Research and Innovation Future Leaders Fellowship (MR/T040912/1), Moorfields Eye Charity Career Development Fellowship and a Lister Institute of Preventative Medicine Fellowship. PJF, APK: Financial support from the UK Department of Health through an award made by the National Institute for Health Research (NIHR) to Moorfields Eye Hospital National Health Service (NHS) Foundation Trust and University College London (UCL) Institute of Ophthalmology for a Biomedical Research Centre (BRC) for Ophthalmology. The sponsors or funding organisations had no role in the design or conduct of this research.

Declaration of competing interest

KVS: none. LRP: Consultant: Twenty Twenty, Eyenovia, Bio Character, Skye Biosciences. JHK: Grant: Pfizer, Inc. PJF: Consultant: Alphasights, GLG, Google Health, Guidepoint, PwC, Santen. APK: Consultant or lecturer: Abbvie, Aerie, Allergan, Google Health, Heidelberg Novartis, Reichert, Santen, Thea.

References

Abe, R.Y., Silva, T.C., Dantas, I., Curado, S.X., Madeira, M.S., de Sousa, L.B., et al., 2020. Can psychologic stress elevate intraocular pressure in healthy individuals? Ophthalmol Glaucoma 3 (6), 426–433.

Adams, B.A., Brubaker, R.F., 1990. Caffeine has no clinically significant effect on aqueous humor flow in the normal human eye. Ophthalmology 97 (8), 1030–1031.

Ajayi, O.B., Ukwade, M.T., 2001. Caffeine and intraocular pressure in a Nigerian population. J. Glaucoma 10 (1), 25–31.

Al Owaifeer, A.M., Al Taisan, A.A., 2018. The role of diet in glaucoma: a review of the current evidence. Ophthalmol Ther 7 (1), 19–31.

Alnawaiseh, M., Lahme, L., Treder, M., Rosentreter, A., Eter, N., 2017. Short-term effects of exercise on optic nerve and macular perfusion measured by optical coherence tomography angiography. Retina 37 (9), 1642–1646.

Ashkenazi, I., Melamed, S., Blumenthal, M., 1992. The effect of continuous strenuous exercise on intraocular pressure. Invest. Ophthalmol. Vis. Sci. 33 (10), 2874–2877.

Avisar, R., Avisar, E., Weinberger, D., 2002. Effect of coffee consumption on intraocular pressure. Ann. Pharmacother. 36 (6), 992–995.

Avunduk, A.M., Yilmaz, B., Sahin, N., Kapicioglu, Z., Dayanir, V., 1999. The comparison of intraocular pressure reductions after isometric and isokinetic exercises in normal individuals. Ophthalmologica 213 (5), 290–294.

Bae, J.H., Kim, J.M., Lee, J.M., Song, J.E., Lee, M.Y., Chung, P.-W., et al., 2020. Effects of consumption of coffee, tea, or soft drinks on open-angle glaucoma: Korea National Health and Nutrition Examination Survey 2010 to 2011. PLoS One 15 (7), e0236152.

Berchuck, S., Jammal, A., Mukherjee, S., Somers, T., Medeiros, F.A., 2021. Impact of anxiety and depression on progression to glaucoma among glaucoma suspects. Br. J. Ophthalmol. 105 (9), 1244–1249.

Bikbov, M.M., Gilmanshin, T.R., Zainullin, R.M., Kazakbaeva, G.M., Arslangareeva II, Panda-Jonas, S., et al., 2020. Prevalence and associated factors of glaucoma in the Russian ural eye and medical study. Sci. Rep. 10 (1), 1–14.

Bonomi, L., Marchini, G., Marraffa, M., Bernardi, P., Morbio, R., Varotto, A., 2000. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt study. Ophthalmology 107 (7), 1287–1293.

Bourne, R.R.A., Taylor, H.R., Flaxman, S.R., Keeffe, J., Leasher, J., Naidoo, K., et al., 2016. Number of people blind or visually impaired by glaucoma worldwide and in world regions 1990 - 2010: a meta-analysis. PLoS One 11 (10), 1–16.

Brody, S., Erb, C., Veit, R., Rau, H., 1999. Intraocular pressure changes: the influence of psychological stress and the Valsalva maneuver. Biol. Psychol. 51 (1), 43–57.

Buckingham, T., Young, R., 1986. The rise and fall of Intra-ocular pressure: the influence of physiological factors. Ophthalmic Physiol. Opt. 6 (1), 95–99.

Buys, Y.M., Harasymowycz, P., Gaspo, R., Kwok, K., Hutnik, C.M.L., Blondeau, P., et al., 2012. Comparison of newly diagnosed ocular hypertension and open-angle glaucoma: ocular variables, risk factors, and disease severity. J Ophthalmol, 757106, 2012.

Bycroft, C., Freeman, C., Petkova, D., Band, G., Elliott, L.T., Sharp, K., et al., 2018. The UK Biobank resource with deep phenotyping and genomic data. Nature 562 (7726), 203–209.
Chan, M.P.Y., Grossi, C.M., Khawaja, A.P., Yip, J.L.Y., Khaw, K.T., Patel, P.J., et al., 2016. Associations with intraocular pressure in a large cohort: results from the UK Biobank. Ophthalmology 123 (4), 771–782.
Chandrasekaran, S., Rochtchina, E., Mitchell, P., 2005. Effects of caffeine on intraocular pressure: the Blue Mountains eye study. J. Glaucoma 14 (6), 504–507.
Charliat, G., Jolly, D., Blanchard, F., 1994. Genetic risk factor in primary open-angle glaucoma: a case-control study. Ophthalmic Epidemiol. 1 (3), 131–138.
Chatterjee, N., Shi, J., García-Closas, M., 2016. Developing and evaluating polygenic risk prediction models for stratified disease prevention. Nat. Rev. Genet. 17 (7), 392–406.
Chiam, N., Baskaran, M., Li, Z., Perera, S., Goh, D., Husain, R., et al., 2018. Social, health and ocular factors associated with primary open-angle glaucoma amongst Chinese Singaporeans. Clin. Exp. Ophthalmol. 46 (1), 25–34.
Choquet, H., Thai, K.K., Yin, J., Hoffmann, T.J., Kvale, M.N., Banda, Y., et al., 2017. A large multi-ethnic genome-wide association study identifies novel genetic loci for intraocular pressure. Nat. Commun. 8 (1), 2108.
Choquet, H., Wiggs, J.L., Khawaja, A.P., 2020. Clinical implications of recent advances in primary open-angle glaucoma genetics. Eye 34 (1), 29–39.
Chua, S.Y.L., Khawaja, A.P., Morgan, J., Strouthidis, N., Reisman, C., Dick, A.D., et al., 2019. The relationship between ambient Atmospheric fine particulate matter (PM2.5) and glaucoma in a large community cohort. Invest. Ophthalmol. Vis. Sci. 60 (14), 4915–4923.
Chung, H.S., Harris, A., Kristinsson, J.K., Ciulla, T.A., Kagemann, C., Ritch, R., 1999. Ginkgo biloba extract increases ocular blood flow velocity. J. Ocul. Pharmacol. Therapeut. 15 (3), 233–240.
Cohen, A.J., Brauer, M., Burnett, R., Anderson, H.R., Frostad, J., Estep, K., et al., 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 389 (10082), 1907–1918.
Coleman, A.L., Stone, K.L., Kodjebacheva, G., Yu, F., Pedula, K.L., Ensrud, K.E., et al., 2008. Glaucoma risk and the consumption of fruits and vegetables among older women in the study of osteoporotic fractures. Am. J. Ophthalmol. 145 (6), 1081–1089.
Collaborative Normal-Tension Glaucoma Study Group, 1998. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am. J. Ophthalmol. 126 (4), 487–497.
Conte, M., Baldin, A.D., Russo, M.R.R.R., Storti, L.R., Caldara, A.A., Cozza, H.F.P., et al., 2014. Effects of high-intensity interval vs. continuous moderate exercise on intraocular pressure. Int. J. Sports Med. 35 (10), 874–878.
Craig, J.E., Han, X., Qassim, A., Hassall, M., Cooke Bailey, J.N., Kinzy, T.G., et al., 2020. Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression. Nat. Genet. 52 (2), 160–166.
Dada, T., Mittal, D., Mohanty, K., Faiq, M.A., Bhat, M.A., Yadav, R.K., et al., 2018. Mindfulness meditation reduces intraocular pressure, lowers stress Biomarkers and modulates gene Expression in glaucoma: a randomized controlled trial. J. Glaucoma 27 (12), 1061–1067.
Dada, T., Lahri, B., Mahalingam, K., Shakrawal, J., Kumar, A., Sihota, R., et al., 2021. Beneficial effect of mindfulness based stress reduction on optic disc perfusion in primary open angle glaucoma: a randomized controlled trial. J Tradit Complement Med 11 (6), 581–586.
Dada, T., Mondal, S., Midha, N., Mahalingam, K., Sihota, R., Gupta, S., et al., 2022. Effect of mindfulness-based stress reduction on intraocular pressure in patients with ocular hypertension: a randomized control trial. Am. J. Ophthalmol. 239, 66–73.
Dervişoğulları, M.S., Totan, Y., Yüce, A., Kulak, A.E., 2016. Acute effects of caffeine on choroidal thickness and ocular pulse amplitude. Cutan. Ocul. Toxicol. 35 (4), 281–286.
Doshi, V., Ying-Lai, M., Azen, S.P., Varma, R., 2008. Sociodemographic, family history, and lifestyle risk factors for open-angle glaucoma and ocular hypertension: the Los Angeles Latino eye study. Ophthalmology 115 (4).
Eckert, A., Keil, U., Scherping, I., Hauptmann, S., Müller, W.E., 2005. Stabilization of mitochondrial membrane potential and improvement of neuronal energy metabolism by Ginkgo biloba extract EGb 761. Ann. N. Y. Acad. Sci. 1056, 474–485.
Edenberg, H.J., 2007. The genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. Alcohol Res. Health 30 (1), 5–13.
Fan, B., Leung, Y., Wang, N., Lam, S., Liu, Y., Tam, O., et al., 2004. Genetic and environmental risk factors for primary open-angle glaucoma. Chin. Med. J. 117 (5), 706–710.
Founti, P., Bunce, C., Khawaja, A.P., Doré, C.J., Mohamed-Noriega, J., Garway-Heath, D. F., et al., 2020. Risk factors for visual field deterioration in the United Kingdom glaucoma treatment study. Ophthalmology 127 (12), 1642–1651.
Fujiwara, K., Yasuda, M., Hata, J., Yoshida, D., Kishimoto, H., Hashimoto, S., et al., 2019. Long-term regular exercise and intraocular pressure: the Hisayama Study. Graefes Arch. Clin. Exp. Ophthalmol. 257 (11), 2461–2469.
Garcia-Medina, J.J., Garcia-Medina, M., Garrido-Fernandez, P., Galvan-Espinosa, J., Garcia-Maturana, C., Zanon-Moreno, V., et al., 2015. A two-year follow-up of oral antioxidant supplementation in primary open-angle glaucoma: an open-label, randomized, controlled trial. Acta Ophthalmol. 93 (6), 546–554.
Garthwaite, G., Bartus, K., Malcolm, D., Goodwin, D., Kollb-Sielecka, M., Dooldeniya, C., et al., 2006. Signaling from blood vessels to CNS axons through nitric oxide. J. Neurosci. 26 (29), 7730–7740.
Gharahkhani, P., Jorgenson, E., Hysi, P., Khawaja, A.P., Pendergrass, S., Han, X., et al., 2021. Genome-wide meta-analysis identifies 127 open-angle glaucoma loci with consistent effect across ancestries. Nat. Commun. 12 (1), 1258.
Giaconi, J.A., Yu, F., Stone, K.L., Pedula, K.L., Ensrud, K.E., Cauley, J.A., et al., 2012. The association of consumption of fruits/vegetables with decreased risk of glaucoma among older African-American women in the study of osteoporotic fractures. Am. J. Ophthalmol. 154 (4), 635–644.
Gillmann, K., Hoskens, K., Mansouri, K., 2019. Acute emotional stress as a trigger for intraocular pressure elevation in Glaucoma. BMC Ophthalmol. 19 (1), 69.
Giurlani, B.P., Obie, L.G., Petersen, C.G., Presley, D.D., 1978. Alcohol and open angle glaucoma - influence on detection, IOP, BP/IOP ratios. J. Am. Optom. Assoc. 49 (4), 409–416.
Grant, A., Leung, G., Aubin, M.-J., Kergoat, M.-J., Li, G., Freeman, E.E., 2021. Fine particulate matter and age-related eye disease: the Canadian Longitudinal study on aging. Invest. Ophthalmol. Vis. Sci. 62 (10), 7.
Grant, A., Leung, G., Freeman, E.E., 2022. Ambient air pollution and age-related eye disease: a systematic review and meta-analysis. Invest. Ophthalmol. Vis. Sci. 63 (9), 17.
Han, Y.S., Kim, Y.W., Kim, Y.J., Park, K.H., Jeoung, J.W., 2020. Alcohol consumption is associated with glaucoma severity regardless of ALDH2 polymorphism. Sci. Rep. 10 (1), 1–9.
Han, X., Steven, K., Qassim, A., Marshall, H.N., Bean, C., Tremeer, M., et al., 2021. Automated AI labeling of optic nerve head enables insights into cross-ancestry glaucoma risk and genetic discovery in >280,000 images from UKB and CLSA. Am. J. Hum. Genet. 108 (7), 1204–1216.
Hanyuda, A., Rosner, B.A., Wiggs, J.L., Willett, W.C., Tsubota, K., Pasquale, L.R., et al., 2020. Low-carbohydrate-diet scores and the risk of primary open-angle glaucoma: data from three US cohorts. Eye 34 (8), 1465–1475.
Harris, A., Malinovsky, V., Martin, B., 1994. Correlates of acute exercise-induced ocular hypotension. Invest. Ophthalmol. Vis. Sci. 35 (11), 3852–3857.
Harris, A., Swartz, D., Engen, D., Beck, D., Evans, D., Caldemeyer, K., et al., 1996. Ocular hemodynamic effects of acute ethanol ingestion. Ophthalmic Res. 28 (3), 193–200.
Heijl, A., Leske, M.C., Bengtsson, B., Hyman, L., Bengtsson, B., Hussein, M., et al., 2002. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch. Ophthalmol. 120 (10), 1268–1279.
Higginbotham, E.J., Kilimanjaro, H.A., Wilensky, J.T., Batenhorst, R.L., Hermann, D., 1989. The effect of caffeine on intraocular pressure in glaucoma patients. Ophthalmology 96 (5), 624–626.
Hirooka, K., Tokuda, M., Miyamoto, O., Itano, T., Baba, T., Shiraga, F., 2004. The Ginkgo biloba extract (EGb 761) provides a neuroprotective effect on retinal ganglion cells in a rat model of chronic glaucoma. Curr. Eye Res. 28 (3), 153–157.
Houle, R.E., Grant, W.M., 1967. Alcohol, vasopressin, and intraocular pressure. Investig. Ophthalmol. Vis. Sci. 6 (2), 145–154.
Hui, F., Tang, J., Williams, P.A., McGuinness, M.B., Hadoux, X., Casson, R.J., et al., 2020. Improvement in inner retinal function in glaucoma with nicotinamide (vitamin B3) supplementation: a crossover randomized clinical trial. Clin. Exp. Ophthalmol. 48 (7), 903–914.
Hunter, D.J., 2005. Gene-environment interactions in human diseases. Nat. Rev. Genet. 6 (4), 287–298.
Ismail, S.A., Mowafi, H.A., 2009. Melatonin provides anxiolysis, enhances analgesia, decreases intraocular pressure, and promotes better operating conditions during cataract surgery under topical anesthesia. Anesth. Analg. 108 (4), 1146–1151.
Jain, A., Zode, G., Kasetti, R.B., Ran, F.A., Yan, W., Sharma, T.P., et al., 2017a. CRISPR-Cas9-based treatment of myocilin-associated glaucoma. Proc. Natl. Acad. Sci. U. S. A. 114 (42), 11199–11204.
Jain, V., Jain, M., Abdull, M.M., Bastawrous, A., 2017b. The association between cigarette smoking and primary open-angle glaucoma: a systematic review. Int. Ophthalmol. 37 (1), 291–301.
Jiang, X., Varma, R., Wu, S., Torres, M., Azen, S.P., Francis, B.A., et al., 2012. Baseline risk factors that predict the development of open-angle glaucoma in a population: the Los Angeles Latino eye study. Ophthalmology 119 (11), 2245–2253.
Jiwani, A.Z., Rhee, D.J., Brauner, S.C., Gardiner, M.F., Chen, T.C., Shen, L.Q., et al., 2012. Effects of caffeinated coffee consumption on intraocular pressure, ocular perfusion pressure, and ocular pulse amplitude: a randomized controlled trial. Eye 26 (8), 1122–1130.
Juronen, E., Tasa, G., Veromann, S., Parts, L., Tiidla, A., Pulges, R., et al., 2000. Polymorphic glutathione S-transferase M1 is a risk factor of primary open-angle glaucoma among Estonians. Exp. Eye Res. 71 (5), 447–452.
Kaimbo Wa Kaimbo, D., Buntinx, F., Missotten, L., 2001. Risk factors for open-angle glaucoma: a case-control study. J. Clin. Epidemiol. 54 (2), 166–171.
Kaluza, G., Strempel, I., Maurer, H., 1996. Stress reactivity of intraocular pressure after relaxation training in open-angle glaucoma patients. J. Behav. Med. 19 (6), 587–598.
Kang, J.H., Pasquale, L.R., Rosner, B.A., Willett, W.C., Egan, K.M., Faberowski, N., et al., 2003. Prospective study of cigarette smoking and the risk of primary open-angle glaucoma. Arch. Ophthalmol. 121 (12), 1762–1768.
Kang, J.H., Pasquale, L.R., Willett, W.C., Rosner, B.A., Egan, K.M., Faberowski, N., et al., 2004. Dietary fat consumption and primary open-angle glaucoma. Am. J. Clin. Nutr. 79 (5), 755–764.
Kang, J.H., Willett, W.C., Rosner, B.A., Hankinson, S.E., Pasquale, L.R., 2007. Prospective study of alcohol consumption and the risk of primary open-angle glaucoma. Ophthalmic Epidemiol. 14 (3), 141–147.
Kang, J.H., Willett, W.C., Rosner, B.A., Hankinson, S.E., Pasquale, L.R., 2008. Caffeine consumption and the risk of primary open-angle glaucoma: a prospective cohort study. Investig. Ophthalmol. Vis. Sci. 49 (5), 1924–1931.
Kang, J.H., Wiggs, J.L., Rosner, B.A., Hankinson, S.E., Abdrabou, W., Fan, B.J., et al., 2010. Endothelial nitric oxide synthase gene variants and primary open-angle

glaucoma: interactions with sex and postmenopausal hormone use. Investig Opthalmology Vis Sci 51 (2), 971.
Kang, J.H., Wiggs, J.L., Rosner, B.A., Haines, J., Abdrabou, W., Pasquale, L.R., 2011. Endothelial nitric oxide synthase gene variants and primary open-angle glaucoma: interactions with hypertension, alcohol intake, and cigarette smoking. Arch. Ophthalmol. 129 (6), 773–780.
Kang, J.H., Willett, W.C., Rosner, B.A., Buys, E., Wiggs, J.L., Pasquale, L.R., 2016. Association of dietary nitrate intake with primary open-angle glaucoma: a prospective analysis from the Nurses' health study and health Professionals follow-up study. JAMA Ophthalmol 134 (3), 294–303.
Kang, J.H., Ivey, K.L., Boumenna, T., Rosner, B., Wiggs, J.L., Pasquale, L.R., 2018. Prospective study of flavonoid intake and risk of primary open-angle glaucoma. Acta Ophthalmol. 96 (6), e692–e700.
Kass, M.A., Heuer, D.K., Higginbotham, E.J., Johnson, C.A., Keltner, J.L., Miller, J.P., et al., 2002. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch. Ophthalmol. 120 (6), 701–713.
Katz, J., Sommer, A., 1988. Risk factors for primary open angle glaucoma. Am. J. Prev. Med. 4 (2), 110–114.
Khawaja, A.P., Cooke Bailey, J.N., Wareham, N.J., Scott, R.A., Simcoe, M., Igo, R.P., et al., 2018. Genome-wide analyses identify 68 new loci associated with intraocular pressure and improve risk prediction for primary open-angle glaucoma. Nat. Genet. 50 (6), 778–782.
Khawaja, A.P., Chua, S., Hysi, P.G., Georgoulas, S., Currant, H., Fitzgerald, T.W., et al., 2020. Comparison of associations with different macular inner retinal thickness parameters in a large cohort: the UK biobank. Ophthalmology 127 (1), 62–71.
Khera, A.V., Chaffin, M., Aragam, K.G., Haas, M.E., Roselli, C., Choi, S.H., et al., 2018. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat. Genet. 50 (9), 1219–1224.
Killer, H.E., Pircher, A., 2018. Normal tension glaucoma: review of current understanding and mechanisms of the pathogenesis. Eye 32 (5), 924–930.
Kim, K.E., Park, K.H., 2018. Macular imaging by optical coherence tomography in the diagnosis and management of glaucoma. Br. J. Ophthalmol. 102 (6), 718–724.
Kim, J., Aschard, H., Kang, J.H., Lentjes, M.A.H., Do, R., Wiggs, J.L., et al., 2021. Intraocular pressure, glaucoma, and dietary caffeine consumption: a gene-diet interaction study from the UK biobank. Ophthalmology 128 (6), 866–876.
Klein, B.E.K., Klein, R., Ritter, L.L., 1993. Relationship of drinking alcohol and smoking to prevalence of open-angle glaucoma: the Beaver dam eye study. Ophthalmology 100 (11), 1609–1613.
Kojima, S., Sugiyama, T., Kojima, M., Azuma, I., Ito, S., 2000. Effect of the consumption of ethanol on the microcirculation of the human optic nerve head in the acute phase. Jpn. J. Ophthalmol. 44 (3), 318–319.
Kumar, D.M., Agarwal, N., 2007. Oxidative stress in glaucoma: a burden of evidence. J. Glaucoma 16 (3), 334–343.
Lamparter, J., Schmidtmann, I., Schuster, A.K., Siouli, A., Wasielica-Poslednik, J., Mirshahi, A., et al., 2018. Association of ocular, cardiovascular, morphometric and lifestyle parameters with retinal nerve fibre layer thickness. PLoS One 13 (5), 1–11.
Latif, N., Naroo, S.A., 2022. Transient effects of smoking on the eye. Contact Lens Anterior Eye 45 (5), 101595.
Le, A., Mukesh, B.N., McCarty, C.A., Taylor, H.R., 2003. Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. Invest. Ophthalmol. Vis. Sci. 44 (9), 3783–3789.
Lee CS, Owen JP, Yanagihara RT, Lorch A, Pershing S, Hyman L, et al. Smoking is associated with higher intraocular pressure regardless of glaucoma: a retrospective study of 12.5 million patients using the Intelligent research in Sight (IRIS®) registry. Ophthalmol Glaucoma. 3(4):253–261.
Lee, A.J., Rochtchina, E., Wang, J.J., Healey, P.R., Mitchell, P., 2003. Does smoking affect intraocular pressure? Findings from the Blue Mountains eye study. J. Glaucoma 12 (3), 209–212.
Lee, J., Sohn, S.W., Kee, C., 2013. Effect of Ginkgo biloba extract on visual field progression in normal tension glaucoma. J. Glaucoma 22 (9), 780–784.
Leighton, D.A., Phillips, C.I., 1970. Effect of moderate exercise on the ocular tension. Br. J. Ophthalmol. 54 (9), 599–605.
Leske, M.C., Warheit-Roberts, L., Wu, S.Y., 1996. Open-angle glaucoma and ocular hypertension: the long Island glaucoma case-control study. Ophthalmic Epidemiol. 3 (2), 85–96.
Leske, M.C., Nemesure, B., He, Q., Wu, S.Y., Fielding Hejtmancik, J., Hennis, A., 2001. Patterns of open-angle glaucoma in the Barbados family study. Ophthalmology 108 (6), 1015–1022.
Lewis, C.J., Hedberg-Buenz, A., DeLuca, A.P., Stone, E.M., Alward, W.L.M., Fingert, J.H., 2017. Primary congenital and developmental glaucomas. Hum. Mol. Genet. 26 (R1), R28–R36.
Li, S., Pan, Y., Xu, J., Li, X., Spiegel, D.P., Bao, J., et al., 2021. Effects of physical exercise on macular vessel density and choroidal thickness in children. Sci. Rep. 11 (1), 2015.
Li, X., Cheng, S., Cheng, J., Wang, M., Zhong, Y., Yu, A.-Y., 2022. Habitual coffee consumption increases risk of primary open-angle glaucoma: a Mendelian randomization study. Ophthalmology 129 (9), 1014–1021.
Lin, H.Y., Hsu, W.M., Chou, P., Liu, C.J., Chou, J.C., Tsai, S.Y., et al., 2005. Intraocular pressure measured with a Noncontact tonometer in an Elderly Chinese population: the Shihpai eye study. Arch. Ophthalmol. 123 (3), 381–386.
Lin, S.-C., Wang, S.Y., Pasquale, L.R., Singh, K., Lin, S.C., 2017. The relation between exercise and glaucoma in a South Korean population-based sample. PLoS One 12 (2), e0171441.
Lockett, A.D., Van Demark, M., Gu, Y., Schweitzer, K.S., Sigua, N., Kamocki, K., et al., 2012. Effect of cigarette smoke exposure and structural modifications on the α-1 antitrypsin interaction with caspases. Mol. Med. 18 (1), 445–454.
Lotfi, K., Grunwald, J.E., 1991. The effect of caffeine on the human macular circulation. Invest. Ophthalmol. Vis. Sci. 32 (12), 3028–3032.
Luksch, A., Resch, H., Weigert, G., Sacu, S., Schmetterer, L., Garhöfer, G., 2009. Acute effects of intravenously administered ethanol on retinal vessel diameters and flicker induced vasodilatation in healthy volunteers. Microvasc. Res. 78 (2), 224–229.
Maas, P., Barrdahl, M., Joshi, A.D., Auer, P.L., Gaudet, M.M., Milne, R.L., et al., 2016. Breast cancer risk from modifiable and Nonmodifiable risk factors among white women in the United States. JAMA Oncol. 2 (10), 1295–1302.
Mabuchi, F., Mabuchi, N., Sakurada, Y., Yoneyama, S., Kashiwagi, K., Iijima, H., et al., 2017. Additive effects of genetic variants associated with intraocular pressure in primary open-angle glaucoma. PLoS One 12 (8), e0183709.
Madjedi, K.M., Stuart, K.V., Chua, S.Y.L., Foster, P.J., Strouthidis, N.G., Luben, R.N., et al., 2022. The association of female reproductive factors with glaucoma and related traits: a systematic review. Ophthalmol Glaucoma 5 (6), 628–647.
Madjedi, K.M., Stuart, K.V., Chua, S.Y., Ramulu, P.Y., Warwick, A., Luben, R.N., et al., 2023. The association of physical activity with glaucoma and related traits in the UK biobank. Ophthalmology. https://doi.org/10.1016/j.ophtha.2023.06.009 (Online ahead of print).
Mahase, E., 2022. Offer patients genetic tests to see if medicines are safe and effective, says Royal College of Physicians. BMJ 376, o821.
Mandrekar, J.N., 2010. Receiver operating characteristic curve in diagnostic test assessment. J. Thorac. Oncol. 5 (9), 1315–1316.
Manolio, T.A., Bailey-Wilson, J.E., Collins, F.S., 2006. Genes, environment and the value of prospective cohort studies. Nat. Rev. Genet. 7 (10), 812–820.
Manolio, T.A., Goodhand, P., Ginsburg, G., 2020. The International Hundred Thousand Plus Cohort Consortium: integrating large-scale cohorts to address global scientific challenges. Lancet Digit Heal 2 (11), e567–e568.
Martin, B., Harris, A., Hammel, T., Malinovsky, V., 1999. Mechanism of exercise-induced ocular hypotension. Invest. Ophthalmol. Vis. Sci. 40 (5), 1011–1015.
Meier, N.F., Lee, D.C., Sui, X., Blair, S.N., 2018. Physical activity, cardiorespiratory fitness, and incident glaucoma. Med. Sci. Sports Exerc. 50 (11), 2253–2258.
Méndez-Ulrich, J.L., Sanz, A., Feliu-Soler, A., Álvarez, M., Borràs, X., 2018. Could white coat ocular hypertension affect to the Accuracy of the diagnosis of glaucoma? Relationships between anxiety and intraocular pressure in a Simulated clinical setting. Appl. Psychophysiol. Biofeedback 43 (1), 49–56.
Miller, V.J., Villamena, F.A., Volek, J.S., 2018. Nutritional Ketosis and Mitohormesis: potential implications for mitochondrial function and human health. J Nutr Metab, 5157645, 2018.
Moreno-Montañés, J., Gándara, E., Moreno-Galarraga, L., Hershey, M.S., López-Gil, J.F., Kales, S., et al., 2022. ACE-vitamin index and risk of glaucoma: the SUN project. Nutrients 14 (23), 5129.
Nathanson, J.A., McKee, M., 1995. Identification of an extensive system of nitric oxide-producing cells in the ciliary muscle and outflow pathway of the human eye. Invest. Ophthalmol. Vis. Sci. 36 (9), 1765–1773.
Natsis, K., Asouhidou, I., Nousios, G., Chatzibalis, T., Vlasis, K., Karabatakis, V., 2009. Aerobic exercise and intraocular pressure in normotensive and glaucoma patients. BMC Ophthalmol. 9, 6.
Oddone, F., Lucenteforte, E., Michelessi, M., Rizzo, S., Donati, S., Parravano, M., et al., 2016. Macular versus retinal nerve fiber layer parameters for diagnosing manifest glaucoma: a systematic review of diagnostic Accuracy studies. Ophthalmology 123 (5), 939–949.
Okimi, P.H., Sportsman, S., Pickard, M.R., Fritsche, M.B., 1991. Effects of caffeinated coffee on intraocular pressure. Appl. Nurs. Res. 4 (2), 72–76.
Okuno, T., Sugiyama, T., Tominaga, M., Kojima, S., Ikeda, T., 2002. Effects of caffeine on microcirculation of the human ocular fundus. Jpn. J. Ophthalmol. 46 (2), 170–176.
Ozkan, B., Yüksel, N., Anik, Y., Altintas, O., Demirci, A., Cağlar, Y., 2008. The effect of caffeine on retrobulbar hemodynamics. Curr. Eye Res. 33 (9), 804–809.
Pan, C.W., Yang, W.Y., Hu, D.N., Xu, J.G., Niu, Z.Q., Yuan, Y.S., et al., 2017. Longitudinal cohort study on the incidence of primary open-angle glaucoma in Bai Chinese. Am. J. Ophthalmol. 176, 127–133.
Park, J.W., Kwon, H.J., Chung, W.S., Kim, C.Y., Seong, G.J., 2011. Short-term effects of Ginkgo biloba extract on peripapillary retinal blood flow in normal tension glaucoma. Kor. J. Ophthalmol. 25 (5), 323–328.
Pasquale, L.R., Kang, J.H., 2009. Lifestyle, nutrition, and glaucoma. J. Glaucoma 18 (6), 423–428.
Pasquale, L.R., Wiggs, J.L., Willett, W.C., Kang, J.H., 2012. The Relationship between caffeine and coffee consumption and exfoliation glaucoma or glaucoma suspect: a prospective study in two cohorts. Invest. Ophthalmol. Vis. Sci. 53 (10), 6427–6433.
Patel, S., Mathan, J.J., Vaghefi, E., Braakhuis, A.J., 2015. The effect of flavonoids on visual function in patients with glaucoma or ocular hypertension: a systematic review and meta-analysis. Graefes Arch. Clin. Exp. Ophthalmol. 253 (11), 1841–1850.
Paulsen, A.J., Pinto, A., Merten, N., Chen, Y., Fischer, M.E., Huang, G.-H., et al., 2021. Factors associated with the macular ganglion cell–inner plexiform layer thickness in a cohort of middle-aged U.S. Adults. Optom. Vis. Sci. 98 (3), 295–305.
Peczon, J.D., Grant, W.M., 1965. Glaucoma, alcohol, and intraocular pressure. Arch. Ophthalmol. 73, 495–501.
Pérez de Arcelus, M., Toledo, E., Martínez-González, M.Á., Sayón-Orea, C., Gea, A., Moreno-Montañés, J., 2014. Omega 3:6 ratio intake and incidence of glaucoma: the SUN cohort. Clin. Nutr. 33 (6), 1041–1045.
Pollock, J.S., Förstermann, U., Mitchell, J.A., Warner, T.D., Schmidt, H.H., Nakane, M., et al., 1991. Purification and characterization of particulate endothelium-derived relaxing factor synthase from cultured and native bovine aortic endothelial cells. Proc. Natl. Acad. Sci. U. S. A. 88 (23), 10480–10484.

Price, E.L., Gray, L.S., Humphries, L., Zweig, C., Button, N.F., 2003. Effect of exercise on intraocular pressure and pulsatile ocular blood flow in a young normal population. Optom. Vis. Sci. 80 (6), 460–466.
Qassim, A., Souzeau, E., Siggs, O.M., Hassall, M.M., Han, X., Griffiths, H.L., et al., 2020. An intraocular pressure polygenic risk score Stratifies multiple primary open-angle glaucoma parameters including treatment intensity. Ophthalmology 127 (7), 901–907.
Qassim, A., Souzeau, E., Hollitt, G., Hassall, M.M., Siggs, O.M., Craig, J.E., 2021. Risk stratification and clinical utility of polygenic risk scores in Ophthalmology. Transl Vis Sci Technol 10 (6), 14.
Quaranta, L., Bettelli, S., Uva, M.G., Semeraro, F., Turano, R., Gandolfo, E., 2003. Effect of Ginkgo biloba extract on preexisting visual field damage in normal tension glaucoma. Ophthalmology 110 (2), 359–362.
Quigley, H.A., 1996. Number of people with glaucoma worldwide. Br. J. Ophthalmol. 80 (5), 389–393.
Quigley, H.A., Enger, C., Katz, J., Sommer, A., Scott, R., Gilbert, D., 1994. Risk factors for the development of glaucomatous visual field loss in ocular hypertension. Arch. Ophthalmol. 112 (5), 644.
Qureshi, I.A., 1995. The effects of mild, moderate, and severe exercise on intraocular pressure in glaucoma patients. Jpn. J. Physiol. 45 (4), 561–569.
Qureshi, I.A., Xi, X.R., Wu, X.D., Zhang, J., Shiarkar, E., 1996. The effect of physical fitness on intraocular pressure in Chinese medical students. Chin. Med. J. 58 (5), 317–322.
Ramdas, W.D., Wolfs, R.C.W., Hofman, A., De Jong, P.T.V.M., Vingerling, J.R., Jansonius, N.M., 2011. Lifestyle and risk of developing open-angle glaucoma: the Rotterdam study. Arch. Ophthalmol. 129 (6), 767–772.
Read, S.A., Collins, M.J., 2011. The short-term influence of exercise on axial length and intraocular pressure. Eye 25 (6), 767–774.
Redondo, B., Vera, J., Molina, R., Jiménez, R., 2020. Short-term effects of caffeine intake on anterior chamber angle and intraocular pressure in low caffeine consumers. Graefe's Arch. Clin. Exp. Ophthalmol. 258 (3), 613–619.
Ren, H., Magulike, N., Ghebremeskel, K., Crawford, M., 2006. Primary open-angle glaucoma patients have reduced levels of blood docosahexaenoic and eicosapentaenoic acids. Prostaglandins Leukot. Essent. Fatty Acids 74 (3), 157–163.
Renard, J.P., Rouland, J.F., Bron, A., Sellem, E., Nordmann, J.P., Baudouin, C., et al., 2013. Nutritional, lifestyle and environmental factors in ocular hypertension and primary open-angle glaucoma: an exploratory case-control study. Acta Ophthalmol. 91 (6), 505–513.
Roberts, R., Chang, C.C., Hadley, T., 2021. Genetic risk stratification: a paradigm shift in prevention of coronary artery disease. JACC Basic to Transl Sci 6 (3), 287–304.
Roddy, G.W., 2020. Metabolic Syndrome is associated with ocular hypertension and glaucoma. J. Glaucoma 29 (9), 726–731.
Russell, G., Lightman, S., 2019. The human stress response. Nat. Rev. Endocrinol. 15 (9), 525–534.
Sears, N.C., Boese, E.A., Miller, M.A., Fingert, J.H., 2019. Mendelian genes in primary open angle glaucoma. Exp. Eye Res. 186, 107702.
Seddon, J.M., Schwartz, B., Flowerdew, G., 1983. Case-control study of ocular hypertension. Arch. Ophthalmol. 101, 891–894.
Shim, S.H., Kim, J.M., Choi, C.Y., Kim, C.Y., Park, K.H., 2012. Ginkgo biloba extract and bilberry anthocyanins improve visual function in patients with normal tension glaucoma. J. Med. Food 15 (9), 818–823.
Shin, D.Y., Jung, K.I., Park, H.Y.L., Park, C.K., 2021. The effect of anxiety and depression on progression of glaucoma. Sci. Rep. 11 (1), 1769.
Siggs, O.M., Qassim, A., Han, X., Marshall, H.N., Mullany, S., He, W., et al., 2022. Association of high polygenic risk with visual field worsening despite treatment in early primary open-angle glaucoma. JAMA Ophthalmol 141 (1), 73–77.
Song, J.E., Kim, J.M., Lee, M.Y., Jang, H.J., Park, K.H., 2020. Effects of consumption of alcohol on intraocular pressure: Korea National health and nutrition examination Survey 2010 to 2011. Nutrients 12 (8), 1–15.
Souzeau, E., Tram, K.H., Witney, M., Ruddle, J.B., Graham, S.L., Healey, P.R., et al., 2017. Myocilin predictive genetic testing for primary open-angle glaucoma leads to early identification of at-risk individuals. Ophthalmology 124 (3), 303–309.
Stein, J.D., Khawaja, A.P., Weizer, J.S., 2021. Glaucoma in adults—screening, diagnosis, and management. JAMA 325 (2), 164.
Stuart, K.V., Madjedi, K., Luben, R.N., Chua, S.Y.L., Warwick, A.N., Chia, M., et al., 2022a. Alcohol, intraocular pressure, and open-angle glaucoma: a systematic review and meta-analysis. Ophthalmology 129 (6), 637–652.
Stuart, K.V., Luben, R.N., Warwick, A.N., Madjedi, K.M., Patel, P.J., Biradar, M.I., et al., 2022b. The association of alcohol consumption with glaucoma and related traits: findings from the UK biobank. Ophthalmol Glaucoma. https://doi.org/10.1016/j.ogla.2022.11.008 (Online ahead of print).
Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., et al., 2015. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 12 (3), e1001779.
Sun, H.-Y., Luo, C.-W., Chiang, Y.-W., Yeh, K.-L., Li, Y.-C., Ho, Y.-C., et al., 2021. Association between PM2.5 exposure level and primary open-angle glaucoma in Taiwanese adults: a nested case-control study. Int. J. Environ. Res. Publ. Health 18 (4), 1714.
Taechameekietichai, T., Chansangpetch, S., Peerawaranun, P., Lin, S.C., 2021. Association between daily niacin intake and glaucoma: National health and nutrition examination Survey. Nutrients 13 (12), 4263.
Tamaki, Y., Araie, M., Nagahara, M., Tomita, K., Matsubara, M., 2000. The acute effects of cigarette smoking on human optic nerve head and posterior fundus circulation in light smokers. Eye 14 (1), 67–72.
Terai, N., Spoerl, E., Pillunat, L.E., Stodtmeister, R., 2012. The effect of caffeine on retinal vessel diameter in young healthy subjects. Acta Ophthalmol. 90 (7), e524–e528.
Tham, Y.-C., Li, X., Wong, T.Y., Quigley, H.A., Aung, T., Cheng, C.-Y., 2014. Global prevalence of glaucoma and projections of glaucoma burden through 2040. Ophthalmology 121 (11), 2081–2090.
Tham, Y.-C., Liao, J., Vithana, E.N., Khor, C.-C., Teo, Y.-Y., Tai, E.-S., et al., 2015. Aggregate effects of intraocular pressure and cup-to-disc ratio genetic variants on glaucoma in a multiethnic Asian population. Ophthalmology 122 (6), 1149–1157.
Toda, N., Nakanishi-Toda, M., 2007. Nitric oxide: ocular blood flow, glaucoma, and diabetic retinopathy. Prog. Retin. Eye Res. 26 (3), 205–238.
Torkamani, A., Wineinger, N.E., Topol, E.J., 2018. The personal and clinical utility of polygenic risk scores. Nat. Rev. Genet. 19 (9), 581–590.
Tran, T., Niyadurupola, N., O'Connor, J., Ang, G.S., Crowston, J., Nguyen, D., 2014. Rise of intraocular pressure in a caffeine test versus the water drinking test in patients with glaucoma. Clin. Exp. Ophthalmol. 42 (5), 427–432.
Tran, J.H., Stuart, K.V., de Vries, V., Vergroesen, J.E., Cousins, C.C., Hysi, P.G., et al., 2023. Genetic associations between smoking- and glaucoma-related traits. Transl Vis Sci Technol 12 (2), 20.
Tseng, V.L., Topouzis, F., Yu, F., Keskini, C., Pappas, T., Founti, P., et al., 2022. Association between dietary Salt intake and open angle glaucoma in the thessaloniki eye study. J. Glaucoma 31 (7), 494–502.
Vera, J., Redondo, B., Molina, R., Bermúdez, J., Jiménez, R., 2019. Effects of caffeine on intraocular pressure are subject to tolerance: a comparative study between low and high caffeine consumers. Psychopharmacology (Berl) 236 (2), 811–819.
Vergroesen, J.E., de Crom, T.O.E., van Duijn, C.M., Voortman, T., Klaver, C.C.W., Ramdas, W.D., 2023. MIND diet lowers risk of open-angle glaucoma: the Rotterdam Study. Eur. J. Nutr. 62 (1), 477–487.
Vo Kim, S., Semoun, O., Pedinielli, A., Jung, C., Miere, A., Souied, E.H., 2019. Optical coherence tomography angiography quantitative assessment of exercise-induced variations in retinal vascular plexa of healthy subjects. Invest. Ophthalmol. Vis. Sci. 60 (5), 1412–1419.
Wang, D., Huang, Y., Huang, C., Wu, P., Lin, J., Zheng, Y., et al., 2012. Association analysis of cigarette smoking with onset of primary open-angle glaucoma and glaucoma-related biometric parameters. BMC Ophthalmol. 12 (1), 59.
Wang, S.Y., Singh, K., Lin, S.C., 2013. Glaucoma and vitamins A, C, and E supplement intake and serum levels in a population-based sample of the United States. Eye 27 (4), 487–494.
Wang, K., Gaitsch, H., Poon, H., Cox, N.J., Rzhetsky, A., 2017. Classification of common human diseases derived from shared genetic and environmental determinants. Nat. Genet. 49 (9), 1319–1325.
Wang, Y.X., Wei, W Bin, Xu, L., Jonas, J.B., 2019. Physical activity and eye diseases. The Beijing eye study. Acta Ophthalmol. 97 (3), 325–331.
Weber, A., Remky, A., Bienert, M., der Velden, KH van, Kirschkamp, T., Rennings, C., et al., 2013. Retrobulbar blood flow and visual field alterations after acute ethanol ingestion. Clin. Ophthalmol. 7, 1641–1646.
Weih, L.M., Mukesh, B.N., McCarty, C.A., Taylor, H.R., 2001. Association of demographic, familial, medical, and ocular factors with intraocular pressure. Arch. Ophthalmol. 119 (6), 875–880.
Westerman, K.E., Pham, D.T., Hong, L., Chen, Y., Sevilla-González, M., Sung, Y.J., et al., 2021. GEM: scalable and flexible gene-environment interaction analysis in millions of samples. Bioinformatics 37 (20), 3514–3520.
Wiggs, J.L., 2012. The cell and molecular biology of complex forms of glaucoma: updates on genetic, environmental, and epigenetic risk factors. Invest. Ophthalmol. Vis. Sci. 53 (5), 2467–2469.
Wiggs, J.L., Pasquale, L.R., 2017. Genetics of glaucoma. Hum. Mol. Genet. 26 (R1), R21–R27.
Williams, P.T., 2009. Relationship of incident glaucoma versus physical activity and fitness in male runners. Med. Sci. Sports Exerc. 41 (8), 1566–1572.
Wilson, M.R., Hertzmark, E., Walker, A.M., Childs Shaw, K., Epstein, D.L., 1987. A case-control study of risk factors in open angle glaucoma. Arch. Ophthalmol. 105 (8), 1066–1071.
Wise, L.A., Rosenberg, L., Radin, R.G., Mattox, C., Yang, E.B., Palmer, J.R., et al., 2011. A prospective study of diabetes, lifestyle factors, and glaucoma among African-American women. Ann. Epidemiol. 21 (6), 430–439.
Wolfs, R.C., Klaver, C.C., Ramrattan, R.S., van Duijn, C.M., Hofman, A., de Jong, P.T., 1998. Genetic risk of primary open-angle glaucoma. Population-based familial aggregation study. Arch. Ophthalmol. 116 (12), 1640–1645.
Wu, S.-Y., Leske, M.C., for the Barbados Eye Study Group, 1997. Associations with intraocular pressure in the Barbados eye study. Arch. Ophthalmol. 115, 1572–1576.
Wu, C.M., Wu, A.M., Tseng, V.L., Yu, F., Coleman, A.L., 2018. Frequency of a diagnosis of glaucoma in individuals who consume coffee, tea and/or soft drinks. Br. J. Ophthalmol. 102 (8), 1127–1133.
Wu, A., Khawaja, A.P., Pasquale, L.R., Stein, J.D., 2020. A review of systemic medications that may modulate the risk of glaucoma. Eye 34 (1), 12–28.
Yamada, K., Hayasaka, S., Matsuoka, Y., 1995. Changes in intraocular pressure after drinking beer in normal eyes and in those with ocular hypertension. Ann. Ophthalmol. 27 (2), 85–88.
Yan, X., Li, M., Song, Y., Guo, J., Zhao, Y., Chen, W., et al., 2016. Influence of exercise on intraocular pressure, Schlemm's canal, and the trabecular meshwork. Invest. Ophthalmol. Vis. Sci. 57 (11), 4733–4739.
Yang, X., Yang, Z., Liu, Y., Chen, X., Yao, B., Liang, F., et al., 2021. The association between long-term exposure to ambient fine particulate matter and glaucoma: a nation-wide epidemiological study among Chinese adults. Int. J. Hyg Environ. Health 238, 113858.

Yoshida, M., Ishikawa, M., Kokaze, A., Sekine, Y., Matsunaga, N., Uchida, Y., et al., 2003. Association of Life-style with intraocular pressure in middle-aged and older Japanese residents. Jpn. J. Ophthalmol. 47 (2), 191–198.
Yoshida, M., Take, S., Ishikawa, M., Kokaze, A., Karita, K., Harada, M., et al., 2014. Association of smoking with intraocular pressure in middle-aged and older Japanese residents. Environ. Health Prev. Med. 19 (2), 100–107.
Zanon-Moreno, V., Ortega-Azorin, C., Asensio-Marquez, E.M., Garcia-Medina, J.J., Pinazo-Duran, M.D., Coltell, O., et al., 2017. A multi-locus genetic risk score for primary open-angle glaucoma (POAG) variants is associated with POAG risk in a Mediterranean population: Inverse correlations with plasma vitamin C and E concentrations. Int. J. Mol. Sci. 18 (11).