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Obesity and Eye Diseases

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Abstract

The prevalence of obesity has reached epidemic proportions in many countries. While its impact on overall health is well documented, less is known about the ocular manifestations of obesity. Amongst different eye diseases, obesity has been linked with age-related cataract, glaucoma, age-related maculopathy, and diabetic retinopathy. Numerous population-based and prospective studies support an association between obesity and risk of age-related cataract. However, the nature and strength of these associations, particularly with the different cataract subtypes, remains to be determined. There is strong evidence that obesity is associated with elevated intraocular pressure, but there is no convincing data to support a more direct association between obesity and glaucomatous optic neuropathy. Studies to date have not found a consistent pattern of association between obesity and risk of age-related maculopathy or diabetic retinopathy. Thus, while obesity may be a risk factor for many ocular conditions, the present literature is inadequate to establish any convincing associations. Furthermore, whether weight loss reduces the risk of eye diseases remains unresolved. Because of the potential public health impact of obesity, there is a greater need to understand its ocular effects.

Keywords

age-related maculopathy; body mass index; cataract; eye disease; glaucoma; obesity; pseudotumor celebri; retinal artery occlusion; retinal vein occlusion; retinopathy

Introduction

Obesity is a major public health problem, with prevalence increasing at staggering rates in many countries.[50, 51, 54, 55, 77, 85, 97, 98] The World Health Organization (WHO) defines obesity as a body mass index (BMI) of 30 kg/m ^{1} or greater, and overweight as individuals whose BMI falls between 25 kg/m ^{1} and 29.9 kg/m ^{1}. (World Health Organization. Controlling the global obesity epidemic. Geneva: World Health Organization; 2002) Different classifications are used for some specific populations, such as the Asians and the children. In Asian populations, it has been proposed that a BMI of 25 kg/m ^{1} or greater should be classified

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as obesity. [98] In children, BMI is classified according to percentiles for age and sex, and children with BMI higher than 95th percentiles for age and sex may be considered as overweight.[30, 39, 133]

Obesity affects a wide spectrum of age groups, from the young[39, 133] to the elderly. [104] In the United States, the prevalence of obesity is 30% in 1999–2000, [51] with 65% of adults, and 10 to 15% of children and adolescents categorized as overweight or obese.[77, 81] The current International Obesity Task Force estimates suggest at least 1.1 billion people are overweight worldwide, and 312 million of them are obese (World Health Organization/International Associatio: redefining obesity and its treatment. Available at:http://www.idi.org.au/obesity_report.htm).

The medical consequences of obesity are numerous. It is an established risk factor for many systemic diseases including coronary heart disease, type 2 diabetes mellitus, hypertension, stroke, dyslipidemia, osteoarthritis, and sleep apnea.[43, 69, 77, 123, 155] Obesity has also been associated with certain types of cancers.[12, 20] One study estimated that obesity is responsible for approximately 40% of endometrial cancers, 25% of renal cancers, and 10% each of colonic and breast cancers. [12] Other obesity-associated co-morbidities include polycystic ovary syndrome, fatty liver as well as depression secondary to social stigmatization and discrimination. [123]

The impact of obesity on health is widespread, and the deleterious effects of obesity on the cardiovascular and metabolic systems are well known. [77] Less well documented, however, are the potential ocular effects of obesity. Obesity has recently been reported to be negatively associated with visual acuity, [10] but the ocular conditions underlying this association and the potential implications are unclear. Amongst different eye diseases, obesity has been associated with cataract,[1, 21, 53, 63, 86, 94, 107, 108, 121, 129, 168, 211, 222] age-related maculopathy,[2, 28, 167, 173] diabetic retinopathy,[8, 24, 83, 114, 171, 207] and glaucoma.[60, 127, 225] However, these associations have not been consistently documented. The purpose of this article is to review the potential ocular effects of obesity.

Obesity and Eye

OBESITY AND CATARACT

Obesity has been proposed to be a risk factor for cataract development, though the exact underlying mechanisms are unclear. The relationship between obesity and cataract has been investigated in many epidemiological studies,[10, 21, 22, 53, 63, 74, 86, 94, 107, 108, 121, 126, 129, 144, 168, 197, 211, 222] but the findings are not universally consistent (Table 1). The strongest evidence are based on prospective data from several large population-based studies demonstrating positive association between obesity and cataract.[63, 73, 86, 107, 168, 211] In 1995 [63] and 2000, [168] the Physicians' Health Study, a randomized trial of 22071 healthy male American physicians aged 40–84 years, reported both overall obesity, measured as BMI, and abdominal adiposity, measured as waist-to-hip ratio (WHR), as independent risk factors for cataract. It was found that at any given level of BMI, a 2-unit higher level predicted a 12% increase risk of cataract. [63] The Nurses' Health Study, a large prospective study of female nurses in 1993, also found a higher rate of cataract surgery for women with BMI levels of 23 or greater compared to women with lower levels. [73] Subsequently, the Nurses' Health and the Health Professionals Follow-up Study generated further results, reporting that obesity increases risk of cataract overall, but in particular, of posterior subcapsular (PSC) type, even after adjusting for variables such as smoking, age and diabetes. [211] Prospective data from the Framingham Eye Study also demonstrates an independent association between greater BMI and higher incident of cortical and PSC opacities. [86] Further support on the positive association between obesity and cataract is derived from cross-sectional data from other population-based,

[1, 21, 94, 121, 129, 222] and hospital-based studies,[126, 197] although not all studies have been consistent. For example, using standardized photography to grade lens opacities, the Beaver Dam Eye Study, a cohort study of almost 5000 white Americans, found no significant associations of obesity with either incident cataract or cataract extraction at the baseline or the 5-year follow-up examination.[108, 110] Nonetheless, 10-year prospective data from this study showed an association between higher BMI and increased risk of PSC cataract in persons without diabetes. [107]

There have also been inconsistencies regarding the types of cataract associated with obesity in these studies. Cortical and PSC cataracts have been most consistently associated with obesity.[1, 21, 121, 129, 222] Among these studies, the Barbados Eye Study in African Americans found higher WHR to be associated with cortical opacities. [129] The Blue Mountain Eye Study in white Australians suggested that obese persons (BMI of 30 kg/m ^{1} or greater) have about half- and twofold increase risk of having cortical and PSC cataracts respectively. [222] In the Age-Related Eye Disease Study (AREDS), both higher BMI and weight gain were found to have significant association with moderate cortical cataract, independent of age and gender. [1] But this association was not statistical significant in the fully adjusted model.

Several plausible pathophysiological mechanisms have been proposed to explain the association of obesity and cataract. One theory suggests that leptin, a 16-kDa pleiotropic cytokine expressed and secreted mainly by adipocytes, [227] is involved in the molecular mechanisms underlying cataract formation. [64] Studies have discovered that individuals with obesity likely exhibit hyperleptinemia and leptin resistance.[59, 78, 79, 149] Leptin has also been found to increase accumulation of reactive oxygen species in various cellular models.[14, 219] This link between obesity, hyperleptinemia and increased oxidative stress has been further reinforced by a subsequent study revealing a strong positive association between BMI and systemic oxidative stress as determined from creatinine-indexed urinary concentrations of 8-epi-prostaglandin F2α. [103] In addition, recent studies have proposed that oxidative stress may play an important pathogenic role in cataract formation.[11, 58, 90, 161, 187, 188, 189, 190] In view of these links, hyperleptinemia associated with obesity may promote cataract formation. Nevertheless, the exact mechanism by which leptin contributes in the process of cataractogenesis is still unclear. Apart from leptin, elevated levels of C-reactive protein and plasma fibrinogen were also found in obese individuals,[32, 52, 71, 209] and recently these markers of inflammation, such as fibrinogen, have been suggested to have association with cataract.[65, 169] Furthermore, obesity has also been linked to cataract by its associated complications such as diabetes,[1, 52, 115, 127, 130, 183] glucose intolerance, insulin resistance,[69] hyperlipidemia and hypertension. They are all known risk factors for cataract,[74, 96, 101, 129, 197, 211, 222] but the primary role of these factors in catarctogenesis is less clear.

While the majority of data suggest that higher BMI is associated with cataract, there has been a body of literature that lower BMI may also be a risk factor for some forms of cataract,[21, 22, 126] particularly in non-white populations.[53, 121, 144] Among Chinese people in the Shihpai Eye Study in Taiwan, for example, whereas higher BMI was associated with cortical opacity, lower BMI was associated with nuclear opacity. [121] In the Tanjong Pagar Survey in Chinese Singaporeans, lower BMI was an independent risk factor for cataract, particularly for cortical cataract. [53] There has been no clear explanation for this pattern of associations. It has been suggested that lower BMI reflects poor nutritional status and malnutrition in developing countries is a potential risk factor for cataract. [198] However, not all Asian data suggest this pattern, and a study in India found no association between lower BMI and age-related cataract.[205]

Finally, there is no evidence that weight loss prevents cataract formation. Although several studies have proposed that weight loss and reduction of abdominal obesity would likely lessen

incidence and costs of cataract,[96, 168] the efficacy of obesity treatment in reducing risk of cataract has never been evaluated in clinical trials.

In summary, based on the current data, obesity is likely associated with cataract. However, there is still controversy regarding which type of cataract is related to obesity. There are varying patterns and strengths of association for different cataract types, suggesting possible existence of distinct etiological pathways for the different types of cataracts. [212] The reason for the disparity of findings may also partly be due to racial/ethnic differences in population groups and use of different grading systems for cataract and lens opacities.

OBESITY AND GLAUCOMA

In contrast to cataract, there are less data addressing the relationship between obesity and glaucoma, although there have been several studies that have provided evidence in support of a positive association between obesity and intraocular pressure (IOP) (Table 2), the strongest risk factor for glaucomatous optic neuropathy (GON).[9, 66, 99, 127, 140, 185]

Most epidemiological studies have been focusing on the association between obesity and IOP or ocular hypertension. Population-based data from several studies have demonstrated independent cross-sectional association between obesity and ocular hypertension.[17, 95, 109, 125, 148, 175, 177, 218, 221] The Beaver Dam Eye Study reported a significantly positive association of IOP with several factors including BMI. [109] This was consistent with findings from a subsequent hospital-based study, indicating that ocular hypertension risk was significantly greater in persons with BMI of 30 or greater, independent of age and sex. [95] Studies of the Asian populations generated similar results.[125, 146, 175, 221] In a large population-based study of 25,216 Japanese aged 14–94 years, a positive association between obesity and ocular hypertension was evident in both longitudinal and cross-sectional analysis, even after controlling for age, gender and blood pressure. [146] This was further reinforced by another large population-based study of Koreans. [125] Some studies further suggest that the association between obesity and ocular hypertension may reflect underlying association between insulin resistance and ocular hypertension, as the association between obesity measures and IOP was not significant after adjustments for glucose and other confounders. [152]

On the contrary, only few studies have directly examined the association between BMI and GON. The limited data generated from these studies demonstrate noticeable inconsistency. Firstly, cross-sectional data from the Barbados Eye Study suggested some protective effect of higher BMI with risk of open-angle glaucoma. [127] The analysis, however, only controlled for age and not other factors, and the possibility of incomplete adjustment for confounders cannot be excluded. Secondly, a hospital-based study, relying on review of medical records, reported that patients with higher BMI were more likely to have a clinical diagnosis of glaucoma on admission. [225] Lastly, in a case-control study, comparing persons with and without glaucoma, no statistically significant difference in BMI was identified. [60]

A clear pathophysiological explanation for the association of obesity with IOP and glaucoma is currently lacking. Both the ‘mechanical’ and ‘vascular’ etiology theories of glaucoma may be related to obesity. With regards to the mechanical theory, [72] obesity has been postulated to exert an effect on IOP by causing excessive intraorbital adipose tissue, increased blood viscosity, increased episcleral venous pressure, and impairment of aqueous outflow facility. [17, 166, 176, 177] Furthermore, ocular hypertension has been associated with obesity-related systemic diseases such as hypertension,[13, 37, 106, 128, 138, 200, 218] diabetes, [152] dyslipidemia, [95] and insulin resistance.[147, 152, 218] Increased blood pressure may lead to an increased filtration fraction of the aqueous humor through elevated ciliary artery pressure,[17, 82, 177] while hyperglycemia may induce osmotic fluid shift into the intraocular space. [141]

Both mechanisms can ultimately result in elevated IOP. On the other hand, the vascular theory suggests that eyes with inherently poor vascular supply to the optic nerve head are more predisposed to damage by elevated or normal IOP.[38, 134] Impaired vascular supply may be related to abnormal ocular blood flow and perfusion instability secondary to alternations in autonomic and endothelial function.[16, 49, 68, 70, 75, 100] Obesity has been shown to cause both vascular endothelial dysfunction[62, 223] and autonomic dysfunction, particularly in people with diabetes.[132, 135] In addition, cellular factors, including neurotropin deprivation, release of excitatory amino acids, and oxidative stress, have also been suggested to contribute to GON on the molecular level.[18, 46, 61, 93, 145, 153, 154, 159, 165, 229] Among these, oxidative stress has recently gained intense interest.[18, 46, 61, 93, 145, 153, 165, 229] Increased oxidative DNA damage was found in the trabecular meshwork of glaucoma patients, [93] and oxidative stress has been postulated to cause proteasome failure and induce human trabecular meshwork degeneration, leading to impairment of the ability of the tissue to modulate outflow resistance. [18] As discussed previously, hyperleptinemia, which is closely related to obesity, is associated with increased oxidative stress.[14, 31, 59, 78, 79, 103, 149, 219] Therefore, theoretically, obesity-associated hyperleptinemia may cause an increase in systemic oxidative stress, priming the glaucoma pathogenetic cascade.[165, 229]

The impact of weight loss on IOP and the development or progression of glaucoma has never been investigated. Although people with ocular hypertension may not develop glaucoma, [105] recent meta-analysis of several methodologically adequate trials revealed that primary prevention of glaucomatous visual field defects in patients with ocular hypertension by using topical pressure lowering agents seems to be effective.[38, 134] This raises the possibility that weight reduction, with adjuvant medical therapy, in obese patients with raised IOP may help preventing the development and progression of GON.

In summary, there is considerable evidence from clinical studies to support an association between obesity with higher IOP. However, current evidence of a direct association between obesity and GON is weak. The possible pathogenic role of obesity in GON remains uncertain as most of the etiologic links are still at the hypothetical level. Further studies are warranted to clarify whether obesity is truly a risk factor for glaucoma.

OBESITY AND AGE-RELATED MACULOPATHY

Age-related maculopathy (ARM) remains a major blinding condition in elderly people, despite the introduction of several new treatment modalities, including photodynamic therapy,[27, 76, 136, 217] novel pharmacological approaches to inhibit angiogenesis[34, 47, 67, 170] and the use of antioxidant supplement.[27, 88]

The relationship between obesity and ARM has been investigated in several studies (Table 3). Hirvela and colleagues [87] were the first to observe a positive association between obesity and ARM. This association was subsequently supported by epidemiological data from several large population-based studies.[36, 108, 167, 184] Prospective data from the Physicians' Health Study demonstrated that the 15-year incidence for visually significant dry ARM was highest in obese men and lowest in men with normal BMI, even after controlling for age and cigarette smoking. [167] However, the study could not find any significant association between obesity and neovascular ARM, which was possibly due to small number of cases in the studied population. The AREDS has reported cross-sectional association between higher BMI and more advanced ARM, as documented from fundus photographs. [2] A more recent report in 2005 among patients with baseline early or intermediate ARM showed that greater BMI was significantly associated with incident geographic atrophy and progression to advanced ARM with visual impairment, even after controlling for multiple factors including age, gender and treatment. [28] These findings are supported by cross-sectional data from the Blue Mountains Eye Study, although the Beaver Dam Eye Study only found this association in women, but not in men. [108] The

Pathologies Oculaires Liées à l'Age (POLA) Study of large number of Europeans found that individuals with obesity have a two-fold increase in risk for developing late but not early ARM, [36] although adjustment for other variables such as smoking were not performed.

The pathophysiological mechanisms accountable for the probable association between obesity and ARM are unclear. ARM is a multifactorial disease with some common downstream pathophysiologic pathways leading to the spectrum of retinal signs seen clinically.[89, 120, 164, 226] Obesity has been hypothesized to be linked to some of these pathways. As discussed previously, obesity may increase systemic oxidative stress secondary to hyperleptinemia.[14, 31, 59, 78, 79, 103, 149, 219] There is compelling evidence that oxidative stress plays an important role in the pathogenesis of ARM.[120, 164, 186, 226] Oxidative damage to lipids in Bruch membrane appears to be important in the etiology of choroidal neovascular ARM.[186] In response to excessive oxidative stress, the RPE cells may detach and migrate into the subretinal space or outer retina and secrete excessive vascular endothelial growth factor (VEGF), eliciting invasion of neovascularization in Bruch membrane. [186] Given this, obesity may have a role in the development of ARM because of its associated hyperliptinemia-induced oxidative stress. Nevertheless, a study examining the association of plasma leptin with ARM found paradoxical results; plasma leptin was negatively correlated with severity of ARM, after controlling for age, sex and BMI. It was suggested by the authors that reduced leptin levels could result in loss of its lipidostatic function in cellular level, leading to an increased intracellular fatty acid accumulation within the lesions found in ARM patients. [44] Studies has also shown that plasma fibrinogen and other markers of inflammation (e.g., C-reactive protein) may be associated with late ARM, [184] suggesting that inflammation may play a role in ARM development. Plasma fibrinogen and C-reactive protein, for example, are elevated in both adults and children with obesity,[6, 206] and may therefore be a potential link between obesity and ARM. Finally, other proposed risk factors for ARM, including hypertension[2, 36, 91, 92, 116] and hyperlipidemia,[112, 210] are also well-known conditions associated with obesity, raising the possibility that obesity may cause ARM by secondary effects from its associated complications.

Apart from an association between BMI and ARM, central obesity, as defined by the waist circumference or WHR, has also been found to increase risk of progression to advanced ARM in one study, [173] although not in another. [143] As with the association of BMI and cataract, there are also some conflicting data, based on a smaller number of studies, indicating that lean body mass may increase risk of ARM.[115, 167, 183]

In summary, there is considerable evidence that supports an association between obesity and ARM. The nature of this association with the different types of ARM and the role of weight loss in preventing the development or slowing the progression of ARM, however, remains to be determined.

OBESITY AND DIABETIC RETINOPATHY

The association between obesity and diabetic retinopathy has been investigated in several studies. Most,[8, 35, 113, 203, 207, 213, 228] but not all,[23, 41, 114, 124, 150] studies have documented a relationship between higher BMI and increased risk of retinopathy (Table 4). Few of these studies, however, have prospective data.[8, 24, 83, 114] A study in Sweden examined 582 young (aged 15–34) individuals with diabetes (79% type 1 diabetes) with 10 years follow-up, and found that individuals with higher BMI developed retinopathy at earlier stage. [83] The EURODIAB Prospective Complications Study of 764 individuals with type 1 diabetes after more than 7 years of follow-up reported WHR as an independent risk factor for diabetic retinopathy. [24] However, conflicting data were generated in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).[113, 114] Although obesity (BMI >31.0 kg/m ^{1} for men and 32.1 kg/m ^{1} for women) was found to associate with progression

and severity of retinopathy, these associations were not statistically significant and were limited to only individuals with older-onset insulin-independent diabetes. [113] On the other hand, for those who were underweight (BMI <20 kg/m ^{1}), a 3-fold increase in risk of developing retinopathy was demonstrated. [114] Underweight has been suggested to be a marker of the more "severe" phase of diabetes, or an indicator of late-onset type 1 diabetes. [113]

There are new data that show obesity is associated with retinopathy signs in the general population and non-diabetic persons. In the Hoorn Study in the Netherlands, WHR was also independently associated with a number of incident retinopathy signs, including retinal hemorrhages, microaneurysms, hard exudates and cotton-wool spots in the non-diabetic general population, although the association with BMI failed to achieve statistical significance. [208]

The underlying pathophysiological mechanisms of the possible association between obesity and retinopathy are not understood. [40] Epidemiological data from various studies have identified hyperlipidemia[25, 26, 29, 33, 48, 111, 117, 147, 150, 193] and hypertension[110, 119, 192, 196] as risk factors for diabetic retinopathy. Both conditions are common risk factors of obesity. In fact, metabolic syndrome, encompassing these conditions, has also been shown to be associated with retinopathy. [213]

However, there is also evidence that obesity may have a more direct role in the development of retinopathy. Several pathogenetic theories of diabetic retinopathy exist based on the potential roles of aldose reductase activity, vasoproliferative factors, oxidative stress, platelet function and blood viscosity. Of these, vasoproliferative factors, such as the vascular endothelial growth factor (VEGF), have recently gained intense interest. The concentration of VEGF has been found to be higher in the vitreous of eyes with proliferative diabetic retinopathy. [5] Serum angiogenic factors, including VEGF, have been observed to be elevated in obese human.[142, 179] These findings provide a potential link between obesity and proliferative diabetic retinopathy. Moreover, oxidative stress has also been suggested to contribute in the pathogenesis of diabetic retinopathy,[19, 156] possibly by inducing over-expression of VEGF and cause features of diabetic retinopathy including retinal neovascularization and macular edema.[19, 178] Finally, as discussed in previous sections, obesity may increase oxidative stress because of its associated hyperleptinemia.[14, 31, 59, 78, 79, 103, 149, 219] High levels of plasma leptin have been found to relate to both hypertensive[4, 172, 194, 203] and diabetic retinopathy.[57, 203] Detailed pathophysiological pathways leading to hypertensive retinopathy has been described elsewhere, [215] but leptin has been postulated to worsen hypertension by activation of the sympathetic nervous system, accelerating the development of hypertensive retinopathy. [80] Positive association between severity of hypertensive retinopathy and plasma leptin, independent of BMI, has been reported. [204] Apart from leptin, other adipocytokines have also been investigated, but the evidence to support their roles in the pathogenesis of retinopathy is currently weak.[42, 45, 56, 137, 220]

The impact of weight loss, particularly in obese individuals, on regression of retinopathy has been inadequately investigated.[174, 195] Lifestyle changes, such as weight loss, has been advocated as a key factor in helping prevent diabetes and to delay diabetic complications including retinopathy in susceptible patients. [174] However, patients with type 1 diabetes and anorexia nervosa with weight loss have also been observed to have higher risk of developing early retinopathy. [195] In spite of the insufficient data, it is generally accepted that weight reduction should be advised in obese diabetic individuals to reduce the risk of cardiovascular disease[118, 180, 181, 182, 191, 201, 202, 216] and possibly diabetic retinopathy. [224]

OBESITY AND OTHER EYE DISEASES

Obesity has been recognized as a significant risk factor for retinal vein occlusion in a very limited number of studies.[7, 214] In the ARIC and Cardiovascular Health Studies (CHS), obese persons were found to have a nearly four-fold increased risk of having retinal vein occlusion, and there was a significant trend of increasing risk across all quartiles of BMI. [214] Moreover, retinal venous and arterial occlusions are known to be associated with hypertension, diabetes mellitus and hypercoagulability or hyperviscosity syndromes.[122, 157, 162, 214] In addition to the known associations of obesity with hypertension and diabetes, several reviews have presented some evidence supporting the association of hypercoagulability disorders with obesity and metabolic syndrome.[3, 151] This provides further support for the possible association between obesity and retinal vascular occlusive diseases.

Other ophthalmic conditions may also be associated with obesity. For example, it has been suggested that obesity may be related to oculomotor nerve palsy. [199] Obesity has also been associated with recurrent lower eyelid entropion. [160] Obstructive sleep apnea syndrome, a common co-morbid condition related to obesity, has been associated with papilledema [158] and floppy eyelid syndrome. [139] Moreover, obesity is also a risk factor for benign intracranial hypertension (pseudotumor cerebri).[15, 102, 163] It has been postulated that central obesity may increase intracranial pressure by increasing intra-abdominal, and subsequently pleural, pressure, with a resultant increase of cardiac filling pressure, impeding venous return from the brain. [15] This suggestion, however, is not agreed by all investigators. [131] And finally, Prader-Willi syndrome, an obesity-associated condition, was found to be related with a number of ocular abnormalities including myopia, astigmatism, amblyopia, strabismus and exotropia. [84]

Future Research

This review suggests that further research is required to fully understand the relationship between obesity and eye diseases. Several lines of investigation are suggested. First, given the growing epidemic of childhood obesity, the lack of data on the ocular effects of obesity early in life needs to be addressed. Secondly, as this review shows, prospective studies are lacking for many of the associations identified from the cross-sectional data. For example, the associations between obesity and IOP, while consistent, are largely based on cross-sectional data, and there are no studies that show obesity is associated with an demonstrable increase in IOP over time. Third, because obesity is closely related to dietary habits, there is a need to study the effect of dietary risk factors on the association of obesity and eye diseases. Fourth, because the criteria for obesity and the dietary habits varies widely between racial/ethnic groups, further studies are needed to address the potential ocular effects of obesity in different racial/ethnic populations. The association between obesity and ARM is an example where studies have only been conducted in white populations. Fifth, the pathophysiological mechanisms underlying the reported associations identified in the epidemiological studies are unknown, and remain as speculations. Thus, additional experimental, cellular or molecular studies may broaden our understanding of the impact of obesity on eye health. Six, most studies have only provided information about how obesity, defined as BMI, weight or WHR, relates to the different eye diseases, and the impact of weight change (weight gain or loss) on eye diseases is less clear. Weight change is more clinically relevant and useful in terms of guiding management. Future epidemiological studies should therefore concentrate on the association of weight change and risk of eye diseases. Finally, in contrast to systemic diseases, there are no clinical trials to demonstrate the potential ocular benefits of weight loss. If weight loss is proven to be an effective method, either as a sole or adjuvant treatment, in delaying the onset or slowing the progression of eye diseases in obese individuals, both clinicians and patients will likely gain additional incentive to battle against this major public health problem.

Conclusion

Obesity is a major public health problem and its impact on ocular health is increasing recognized. Associations of obesity with cataract, glaucoma, age-related maculopathy and retinopathy have been reported with varying degree of certainty. The inconsistency of results, combined with the deficiency of robust data, suggest that further investigations are required to clarify these associations. The efficacy of obesity treatment in reducing the risk of eye diseases is also unknown, but studies in this area may provide important insight for the potential use of weight loss strategies to reduce the burden of eye diseases in individuals with obesity.

Method of Literature Search

A systematic MEDLINE search on National Institute of Health's PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB=pubmed) with coverage up to 18 August 2005 was conducted initially using the following keywords: *"obesity, body mass index, waist-to-hip ratio, weight, risk factor"* in various combinations with *"eye (368 citations), eye disease (725), ocular (225), cataract (66), lens opacity (48), glaucoma (37), intraocular pressure (32), maculopathy (13), diabetic retinopathy (24), hypertensive retinopathy (34), retinal arterial occlusion (8), retinal venous occlusion (10)"*. After review of abstracts, relevant articles were retrieved and reviewed. All English articles were read, and for the relevant non-English articles, the English abstracts were reviewed. Bibliographies of these articles provided further references, including books and internet-based data.

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Table 1

Population-based Studies Investigating the Relationship between Obesity and Cataract

Study			Definition of cataract	Summary of main findings	Reference
Year	**Type**	**Population**			
2002	P	The Nurses' Health Study and the Health Professionals Follow-up Study	Incident cataract extractions	Higher BMI associated with overall cataract overall (36%, RR1.36; 95% CI 1.23–1.49) after adjustment for smoking, age and lutein/zeaxanthin intake, and with PSC cataract (RR 1.68 (95% CI 1.30–2.17), after adjusting for diabetes Obesity not associated with nuclear cataract.	211
2000	P	The Physicians' Health Study	Incident cataract and cataract surgery	Higher BMI (RR 1.25) and WHR (RR 1.31) associated with cataract, after adjustment for cigarette smoking, alcohol consumption, exercise, multivitamin use, diabetes, and systolic blood pressure	168
1995	P	The Physicians' Health Study	Incident cataract or cataract extraction	Higher BMI (RR 2.1) associated with incident cataract Stronger associations noted for PSC and nuclear cataracts	63
1998	P	The Framingham Eye Study	Eye examination and lens photographs	Higher BMI associated with cortical (OR 3.24) and PSC (OR 1.24) opacities after adjustment for age, sex, education, diabetes, and smoking.	86
1993	P	The Nurses' Health Study with 5 year follow-up	Incident cataract extraction	Higher BMI associated with higher rate of cataract extraction in women	73
1998	P	The Beaver Dam Eye Study Cohort	Eye examination, lens photography	Higher BMI associated with increased risk of PSC cataract in persons without diabetes	107
2001	C	The Age-Related Eye Disease Study (AREDS)	Eye examination Lens photography	Higher BMI (OR 1.40) and weight gain (OR 1.51) associated with moderate cortical cataract after adjustment for age and gender	1
2001	C	The Beaver Dam Eye Study	Eye examination Lens photographs	WTH ratio was more strongly associated with cortical and PSC opacities than BMI, but the relationships not significant	108
1997	C	The Beaver Dam Eye Study	Incident cataract extraction	BMI not associated with cataract extraction	110
2003	C	The Blue Mountains Eye Study	Lens photographs	Higher BMI associated with cortical (OR 1.6) and PSC cataract (OR 2.1)	222
1999	C	The Barbados Eye Study	Lens Opacities Classification System II on eye examinations	Higher WHR associated with cortical opacities after adjustment for age (OR 1.36)	129
2003	C	The Nurses' Health Study	Lens Opacification Classification System III	Higher BMI (OR 2.5) and abdominal adiposity (OR 2.3) associated with PSC opacities, but not with nuclear and cortical cataract	94
1999	C	The Salisbury Eye Evaluation project	Eye examinations Lens photography Wilmer grading scheme	Higher BMI associated with cortical cataract (adjusted OR1.26), but lower BMI (OR 1.13) associated with nuclear cataract, after adjustment for age, race, sex, stature, alcohol consumption, and average annual ultraviolet blue exposure BMI not associated with PSC opacities.	21
2003	C	The Tanjong Pagar Survey	Eye examinations Lens Opacity Classification System III	Lower BMI associated with any cataract (OR 2.3) and cortical cataract (OR 1.8) after adjustment for age, sex and other factors.	53

Study			Definition of cataract	Summary of main findings	Reference
Year	**Type**	**Population**			
2005	C	The Shihpai Eye Study	Lens Opacities Classification System III grade of more than 2	Higher BMI associated with lower risk of nuclear (OR 0.73) and higher risk of cortical (1.52) opacities No association with PSC opacity	121
1982	C	Survey from 1269 participants in Punjab	Incident cataract survey	Lower body weight associated with higher prevalence of cataract	22

BMI = Body Mass Index, PSC = Posterior Subcapsular, WTH = Waist-To-Hip, OR = Odds Ratio, RR = Relative Risk, CI = Confidence Interval, P = Prospective, C = Cross-sectional

Table 2

Studies Investigating Relationship between Obesity and Glaucoma or Intraocular Pressure

Study			Definition of glaucoma	Summary of main findings	Reference
Year	**Type**	**Population**			
1995	PB, C	The Barbados Eye Study	IOP Visual field defect Optic disc damage	Higher BMI associated with lower risk of open-angle glaucoma (high vs low BMI quartiles with OR 0.39) after adjustment for age	127
1999	HB, C	288 control subjects 129 patients with glaucoma	Visual defects IOP	BMI not associated with glaucoma.	60
1994	HB, C	20011 males 9083 females	Medical records	Highest BMI associated with glaucoma	225
2002	PB, C	13212 healthy Koreans aged 20–70	IOP measurement by applanation tonometry	Higher BMI associated with higher IOP after controlling for age, sex, and mean blood pressure in men ($p<0.05$), but association not significant in women	125
2000	PB, C	25216 Japanese aged 14–94 years	IOP measurement by applanation tonometry	Higher BMI associated with higher IOP after adjustment for age, gender and blood pressure in cross-sectional analysis (IOP 11.3 with BMI<20 vs IOP 12.2 with BMI≥25; $p<0.0001$) Increased weight associated with higher IOP, even after adjustment for age, gender, initial BMI, initial blood pressure and initial IOP in longitudinal analysis	146
1997	PB, C	The Barbados Eye Study	IOP measurement by applanation tonometry	Higher BMI associated with higher IOP	218
1992	PB, C	The Beaver Dam Eye Study	IOP measurements by applanation tonometry	Higher BMI associated with higher IOP	109
1986	PB, C	93703 Japanese persons	IOP measurements by applanation tonometry	Higher obesity index associated with higher IOP	177
2005	HB, C	943 healthy persons	IOP measurement by applanation tonometry	Insulin resistance indices showed positive associations with IOP, even after multiple adjustments. Abdominal obesity associated with higher IOP in men, but not in women, and not statistically significant after adjustments	152
2003	HB, C	649 Japanese aged 29–79 years	IOP measurement by applanation tonometry	Higher BMI associated with higher IOP in both men and women after adjustment for alcohol consumption, cigarette smoking, habitual exercise and coffee consumption, with systolic blood pressure	221
2001	HB, C	990 persons aged ≥ 40 years old	IOP measurement by applanation tonometry with ocular hypertension defined as IOP ≥ 21mmHg	Higher BMI associated with ocular hypertension (OR ≥ 4.2) after adjustment for age and sex	95

BMI = Body Mass Index, IOP = Intraocular Pressure, OR = Odds Ratio, PB = Population-based, HB = Hospital-based, P = Prospective data, C = Cross-sectional data

Table 3

Studies Investigating Relationship between Obesity and Age-Related Maculopathy

Type of study			Defintion of age-related maculopathy	Summary of main findings	Reference
Year	**Type**	**Population**			
2001	PB, P	The Physician Health Study	Incident ARM	Higher BMI associated with incident visually significant dry ARM (rate ratio 2.15), after adjustment for age and cigarette smoking	167
2005	HB, P	Age-Related Eye Disease Study (AREDS) 3295 patients with baseline early/ intermediate ARM	Fundus photographs	Higher BMI (OR 1.93) associated with geographic atrophy and risk for progression from early/intermediate to advanced ARM, after adjustment for age, gender, and treatment group	28
2000	HB, P	AREDS	Color fundus photographs	Higher BMI associated with more advanced ARM	2
2003	HB, P	366 persons aged >60 years	Fundus photography	Higher BMI (RR 2.32) and larger abdominal circumference (RR 2.04) associated with progression to advanced ARM	173
1998	PB, C	The Blue Mountains Eye Study	Retinal photographs Wisconsin Age-Related Maculopathy Grading System	Higher BMI (OR 1.78) and plasma fibrinogen level (OR 6.7) associated with ARM	184
1996	PB, C	500 participants aged 70 or older	Fundus photographs or ophthalmoscopic findings	Higher BMI in men associated with higher prevalence of ARM in all age groups (48% for BMI ≥27.5 vs 34% for BMI ≤27.5, p = 0.019).	87
2001	PB, C	The Beaver Dam Eye Study	Retinal photographs	Higher BMI associated with early (OR 1.59), but not late ARM in women, but not men	108
2001	PB, C	The POLA Study 2584 European aged 60–95	Eye examination and fundus photographs	Higher BMI associated with increased risk of late ARM (2.29-fold) and retinal pigmentary abnormalities (1.54-fold)	36

ARM = Age-related Maculopathy, BMI = Body Mass Index, OR = Odds Ratio, RR = Relative Risk, CI = Confidence Interval, PB = Population-based, C = Cross-sectional data, P = Prospective data

Table 4

Studies Investigating Relationship between Obesity and Diabetic Retinopathy

Study			Definition of diabetic retinopathy	Summary of main findings	Reference
Year	Type	Population			
2003	PB, P	The Hoorn Study	Ophthalmoscopy and fundus photography	Higher WHR (OR 8.67) associated with retinopathy, but not for BMI	208
2003	PB, P	Diabetes Incidence Study in Sweden (DISS) (79% type 1 diabetes)	Retinal photographs	Higher BMI associated with earlier development of retinopathy (RR 1.11)	83
2001	PB, P	EURODIAB Prospective Complications Study (persons with type 1 diabetes)	Retinal photographs	Higher WHR (OR 1.32) associated with diabetic retinopathy	24
1986	PB, P	1031 persons with diabetes mellitus	Incident diabetic retinopathy Ocular examination	Obesity associated with increased risk of retinopathy (hazard ratio 2.01)	8
2001	PB, C	Diabetes Control and Complications Trial (DCCT)	Ocular Examination	Higher BMI (OR 1.11) associated with diabetic retinopathy after adjustment for metabolic control	228
2002	PB, C	The Hoorn Study	Ophthalmologic examination and fundus photography	Higher BMI (OR 1.3) associated with retinopathy	207
1984	PB, C	Wisconsin Epidemiologic Study of Diabetic Retinopathy	Ocular examination and retinal photography	Small body mass associated with more severe retinopathy	114
1998	PB, C	911 of 6553 participants from survey on the Indian Ocean island of Mauritius	Retinal photographs with grading according to modified Airlie House criteria	Lower BMI associated with retinopathy	41
2005	HP, C	156 persons with diabetes mellitus	Ocular examinations	Higher BMI associated with increased prevalence of retinopathy (40.8% in BMI≤25, 63.4% in BMI 26–29.9, 63.6% in BMI≥30)	101

BMI = Body Mass Index, OR = Odds Ratio, RR = Relative Risk, CI = Confidence Interval, PB = Population-based, HP = Hospital-based, P = Prospective data, C = Cross-sectional data