Role of excessive weight in intraocular pressure: a systematic review and meta-analysis

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ABSTRACT

Objective This systematic review and meta-analysis aimed to analyse the effect of excess body weight on intraocular pressure (IOP) values.

Method and analysis A literature search from PubMed, Medline and ScienceDirect Databases on 18 May 2023 was conducted by three reviewers, then filtered each study based on inclusion and exclusion criteria. For the quality assessment of included studies, the Newcastle–Ottawa Scale was adapted. Meta-analysis was performed using RevMan V.5.4 by entering the IOP values of each group to measure the mean difference.

Results From 2656 studies, there were 9 studies that matched the criteria and then were included to perform a quantitative meta-analysis. The results showed a mean difference of 0.93 (95% CI: 0.67 to 1.18) of the excessive weight group against the normal weight group. This suggests that there is a significant relationship between excess body weight and increasing values of IOP.

Conclusion It can be concluded that excessive body weight tends to lead to higher IOP, which means that high IOP becomes a major risk factor for glaucoma.

INTRODUCTION

The eyesight is one of the most important senses for human life.1 The eye is an organ with various complex structures; therefore, injuries or disorders that affect eye homeostasis can cause various vision problems and can lead to blindness, where the imbalance of intraocular pressure (IOP) is one of the risk factors that can cause many eye disorders.2 IOP is a value of the pressure on fluid inside the eyeball.3 An IOP value is determined by the volume of aqueous humour contained in the intraocular tissue of the eye. Increased IOP can damage the structures inside the eyeball, which occurs if there is an imbalance between the production and outflow of the aqueous humour; therefore, it becomes one of the main risk factors for glaucoma and blindness.4

Glaucoma is the second leading cause of irreversible blindness.5 Glaucoma is characterised by the death of ganglion cell, loss of nerve axons, damage to the optic nerve and loss of visual ability of the eye.6 According to data from the WHO in 2010, it was estimated that 3.2 million people were blind due to glaucoma and predicted to increase continuously.7 Currently, there are several approaches to overcome the problem of blindness due to glaucoma by maintaining the balance of IOP value within normal or lowering it back to its normal value. Several current studies show that various types of lifestyle, one of which related to body weight, have a significant relationship with increased IOP.8

Excessive weight, especially obesity, is currently a major health problem in the world and is linked to more deaths worldwide than underweight. According to data from the WHO in 2016, it is estimated that around 1.9 billion adults over 18 years are overweight (25 kg/m2), and 650 million of them are obese (30 kg/m2).9 The prevalence of obesity, based on data from the Basic Health Research in Indonesia on 2018, for people aged over 18 years increased from 14.8% to 21.8%.10
Obesity is also known as a major risk factor for several diseases such as type 2 diabetes mellitus, hypertension, stroke and osteoarthritis. Several eye diseases are also associated with overweight, such as cataracts, glaucoma, diabetic retinopathy and age-related macular degeneration. In addition, obesity is also believed to elevate the risk of increased IOP, which might further cause glaucoma.11

Various studies have reported the relationship between obesity and IOP. Some of these studies reported there is significant increase of IOP due to excess of weight on a patient; one of these studies is the large cohort of Korean adults attending health screening visits, where it was found that IOP gradually increased significantly with the increase of body weight and adiposity on patients.12 However, some studies report a negative correlation between excess body weight and IOP. Cakmak et al report that overweight and obese patients displayed a reduced risk of low mean ocular perfusion pressure (MOPP) value, which means that a low MOPP value is associated with increased risk of glaucoma.13 In accordance with the ambiguous results of some studies, this analysis aims to conclude the relationship between excess body weight and IOP values through various studies using a systematic study which will be concluded in the form of a meta-analysis.

**METHOD**

**Literature search**

In this systematic review, a literature search was conducted on 18 May 2023 by three reviewers (MAGM, ATFZ and GBL) from various databases, including PubMed, Medline and ScienceDirect, using the keywords (obesity OR (body mass index) OR (BMI) OR (anthropometric) OR (bodyweight) OR (body fat) OR (adiposity) OR (intra-abdominal fat)) AND (((glaucoma) OR (Primary open angle glaucoma)) OR (intraocular pressure) OR (IOP)). In addition, some valid studies outside of the database will be included if they meet the criteria.

**Selection of studies**

The study criteria that will be included in this systematic study are as follows: (1) published at least 15 years; (2) the research design is an observational study (cohort, case–control or cross-sectional); (3) the language used is Indonesian or English; (4) exposure is excess body weight (body mass index (BMI), SD score); (5) contrast is normal weight; (6) outcome is the value of IOP and (7) abstract is available.

On the other hand, exclusion criteria include the sample population with a history of systemic diseases that might affect IOP (including diabetes, hypertension, thyroid disorders), family history of glaucoma, pharmacological treatment and history of eye disease (history of glaucoma and uveitis, optic anomalies, eye trauma, history of intraocular surgery). Furthermore, exposures that did not use valid body weight parameters, contrast that included underweight and studies without IOP data would also be excluded.

After a period of searching, duplicate studies from various sources will be identified and excluded, and filtering of literature studies will be done by reading the titles and abstracts of all studies obtained from the search. The literature review screening process is carried out by at least two independent review authors. Literature studies which meet the eligibility criteria will be included, while those that do not meet the eligibility criteria will be excluded for reasons listed. Conflicts in the grouping of studies will be discussed together until a final decision is reached. The results of the literature study screening will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-analyses rules.

**Data extraction**

Collection of data will be carried out on all included studies. The data to be collected include the following: (1) main author; (2) year of publication; (3) place where the research is conducted; (4) number of samples; (5) sample characteristics (age); (6) type of exposure and (7) outcome type.

Collection of data is carried out by one review author independently, and then cross-examination will be carried out by other review authors. If the included literature study contains incomplete data, the review authors will contact the author of the study; if the author does not respond, the study is then excluded with the agreement of the review authors.

Excess body weight is defined as a group that has a BMI that exceeds the normal limit such as overweight, type 1 obesity and so on, according to the BMI classification used in each study, which will later be attached to the collection of data table.

**Quality assessment**

Reviewers assessed the methodological quality of each study using the Newcastle–Ottawa Quality Assessment Scale (for case–control, cohort and adapted for cross-sectional studies). Studies were not excluded on the basis of quality. The Newcastle–Ottawa Assessment of Bias measures quality according to a star-based system; there is a separate scoring system for cohort, case–control and cross-sectional studies. Each study is judged on three categories: selection of study groups, comparability of groups, and the ascertainment of either the exposure of interest in case–control studies or outcome of interest in cohort studies. Classification of the studies’ quality was based on Agency for Healthcare Research and Quality standards. Good-quality studies receive three or four stars in the selection domain; one or two stars in the comparability domain; and two or three stars in the outcome domain. Fair-quality studies receive two stars in the selection domain; one or two stars in the comparability domain; and two or three stars in the outcome domain. Poor-quality studies receive zero or one star in the selection
domain; zero star in the comparability domain; and zero or one star in the outcome domain.14

Statistical analysis
The data obtained are processed using Review Manager V.5.4. Meta-analysis was performed by including IOP values in the overweight and normal weight groups to measure the mean difference (95% CI) of the studies that met the criteria for inclusion through quantitative analysis and visually displayed by a forest plot. Heterogeneity of statistical analysis is seen from the value of $\tau^2$. Fixed-effects model is used if $I^2<50\%$, while random-effects model is used if $I^2>50\%$.

Publication bias
Publication bias is evaluated subjectively by looking at the funnel plot. A funnel plot is a graph designed to check for the existence of publication bias and is commonly used in systematic reviews and meta-analyses. In addition, for situations where the heterogeneity was too great ($I^2\geq80\%$), the Duval and Tweedie’s trim-and-fill analysis was performed to recalculate effect sizes after removing all studies that could have caused publication bias.

RESULT

Literature search and result of screening
In this systematic study, a search of literature studies from various databases, namely PubMed, Medline and ScienceDirect, using the keywords, has been conducted. A total of 2656 studies were obtained, which were then filtered according to predetermined criteria.

Prior to screening, 306 duplicate studies were excluded. Furthermore, 2344 study titles and abstracts were screened independently by three reviewers (MAGM, ATFZ and GBL). A total of 2328 studies were excluded because they did not meet the predetermined criteria. The next 16 studies were screened by reading the full text. As a result, three studies were excluded because full-text was not available and four studies were excluded because data were not matched with our criteria; therefore, the remaining nine studies met the criteria and were included for qualitative and quantitative analyses. Full details of the search and filtering results are presented in figure 1.

Literature search characteristics of the eligible studies
The nine included studies were primary studies conducted in six different countries with a total sample 22,920. Of the nine studies, four studies used a cross-sectional design, two case–control and three cohort. All studies assessed one of the outcomes in the form of IOP values.

BMI classification from various studies uses different indicators: five studies use the BMI standard criteria by the European WHO, two studies use the BMI standard criteria by the Asian WHO, one study uses the Centers for Disease Control BMI-for-age percentile growth charts and one study uses the SD score BMI. Full details of the characteristics of the included studies are presented in table 1.

Quality assessment result
The quality ratings of the nine included studies were represented by the total stars obtained for each study from the range 0 to 10 for cross-sectional studies and range 0–9 for cohort and case–control studies. In general, the quality of the included studies was good: only one study was considered as poor, one study as fair and good quality found mostly in the seven studies. The complete details of the quality assessment are presented in online supplemental table 1.

Statistical test results (meta-analysis)
Continuous data in the form of the IOP values from each group were collected from nine included studies. Furthermore, the data are entered in a statistical test using the Review Manager V.5.4 application to see the mean difference using the random-effects model. During meta-analysis, we did a subgroup analysis by dividing the studies into three groups based on the design, which is a cross-sectional, case–control or cohort. The results showed total mean difference of 0.93 (95% CI 0.67 to 1.18). The overall effect was $Z=7.15$ ($p<0.00001$) and heterogeneity was $\tau^2=0.08$; $\chi^2=86.94$; $df=11$ ($p<0.00001$); $I^2=87\%$. These results are presented in the form of a forest plot in figure 2A.
Besides, we did a subgroup analysis by dividing the groups of studies into three based on the classification of body weight, which is overweight, obese and morbidly obese, and examined their effect on the patient’s IOP. The results showed subtotal mean difference of 0.60 (95% CI 0.48 to 0.72) in the overweight subgroup, 1.02 (95% CI 0.60 to 1.44) in the obese subgroup and 1.25 (95% CI 0.96 to 1.54) in the morbidly obese subgroup. These subgroup result analyses indicate that the higher the weight classification of the sample, the higher their IOP values become. These results are presented in the form of a forest plot in figure 2B.

**Publication bias**

The funnel plot in figure 2C shows the asymmetrical shape of the study distribution, suggesting the possibility of publication bias.

**DISCUSSION**

The results of the meta-analysis showed that people who have excess body weight will have higher IOP values than the normal weight sample (0.93 (95% CI: 0.67 to 1.18)). This finding is in line with a meta-analysis by Liu et al, who examined the relationship between body adipose levels and the risk of glaucoma. From 15 included studies, it was found that overweight samples assessed by BMI, waist circumference and adiposity had a 1.19 (95% CI: 1.04 to 1.37) times higher risk of suffering from glaucoma caused by an increase in IOP. The conclusion of the meta-analysis by Liu et al illustrates that body adipose levels associated with excess body weight can increase the risk of increased IOP that might lead to glaucoma.15 This was found to be in line with previous primary studies which reported that there was a difference in scores between overweight patients compared with those with normal weight and IOP values.16–22

Besides, based on the subgroup analysis of dividing the studies into overweight, obese and morbidly obese subgroups, it showed a subtotal mean difference of 0.60 (95% CI 0.48 to 0.72) in the overweight subgroup, 1.02 (95% CI 0.60 to 1.44) in the obese subgroup and 1.25 (95% CI 0.96 to 1.54) in the morbidly obese subgroup, which indicated that the higher patient weight classification will lead to higher IOP values.

‘Excess body weight can increase IOP’ is explained in two theories, namely ‘mechanical’ and ‘vascular’. Based on the mechanical theory, obesity can lead to an increase in IOP by causing an increase in intraorbital adipose tissue, blood viscosity and episcleral venous pressure,23 where fat accumulation in obesity leads to a decrease in aqueous humour outflow.24 The vascular theory suggests
Figure 2  (A) Forest plot of subgroup meta-analysis on the effect of excessive weight on intraocular pressure values. (B) Forest plot of subgroup meta-analysis on the effect on intraocular pressure values. (C) Funnel plot of meta-analysis on the effect of excessive weight on intraocular pressure values. Each black circle represents a study that is distributed based on the x-axis: mean difference (MD) and the y-axis: SEM difference.
that eyes with poor vascular supply to the optic nerve will be more susceptible to damage when having elevated IOP. Changes in autonomic and endothelial function can result in abnormal blood flow to the eye and unstable perfusion that impairs vascular supply. Obesity was found to be a factor of vascular endothelial dysfunction and autonomic dysfunction. The mechanical theory is supported by Stojanov et al, who reported on the conclusion of their research, that the sample with BMI >30 kg/m² had an average IOP value of 15.96 mm Hg compared with those with a normal BMI (18.5–24.9 kg/m²) who only have an average IOP of 12.99 mm Hg. The increase in IOP values in obese patients is associated with a buildup of retrobulbar adipose tissue (RAT) volume, where the obese sample has a thicker RAT (mean 6.23 cm³) than in the normal sample which has a mean RAT of 4.85 cm³. Furthermore, Stojanov et al explained that RAT can affect IOP due to the ‘mass effect’ mechanism, where the buildup of RAT can directly or indirectly affect episcleral venous pressure which can cause outflow dysfunction in Schlemm’s canal, further triggering an increase in IOP.

In addition, increased blood viscosity in obese samples in the form of an increase in blood cell count, haemoglobin and haematocrit was associated with resistance to outflow in the episcleral vein, further causing an increase in venous pressure that might reduce aqueous humour outflow, resulting in an increase in IOP.

In addition, a study by Oner and Karadağ stated that in obese patients, there was a thinning of choroidal thickness which results in abnormalities in the choroidal vascular bed that had an impact on ocular pulse amplitude (OPA). OPA itself can show choroidal flow perfusion and intraocular blood flow with a measurement using optical coherence tomography or dynamic contour tonometry (DCT). OPA is defined as the difference between diastolic and systolic IOP which reflects choroidal pulsatile flow in the form of a difference in IOP. However, in the study by Oner and Karadağ, it was found that there was a decrease in the value of OPA. In the obese group measured using DCT, OPA was found to be 2.19±0.53 mm, while in normal weight patients, OPA was found to be 2.10±0.74 mm. This shows that ocular blood flow is impaired in the obese group that is shown by a decrease in OPA, which can cause obese patients to experience accelerated visual damage due to glaucoma. This is also supported by a study done by Vulfsteke et al, who reported that lower OPA values in obese patients as measured by DCT were associated with visual field defects due to severe glaucoma, and increased risk factors for visual organ defects. In a study by Karadag et al, it was also found that the lowest OPA values were experienced in the obese group (average 2.1 mm) and in the normal weight group (2.7 mm). Therefore, the decreased OPA value in obese subjects may indicate that the obese group is more prone to experiencing increased IOP values and glaucoma who are more likely to suffer from accelerated visual disability than normal weight subjects without glaucoma.

The vascular theory is based on several studies that have examined the mechanisms underlying the microvascular changes associated with obesity, which obesity is known to cause inflammation that results in the release of many cytokines. Findings of Yilmaz et al found that adipose accumulation in obese patients causes an increase in the secretion of many molecules such as endothelin-1 (ET-1) and angiotensin-II, and also decrease of nitric oxide (NO). NO, an endothelium-derived vasodilator molecule, was found to be decreased in obesity and has been shown to result in impaired dilatation of the vasculature. NO vasodilator molecule of endothelial origin regulates the ocular blood flow and has a positive effect on IOP regulation. NO signals regulate aqueous humour outflow from the anterior chamber through the trabecular meshwork and Schlemm’s canal by decreasing the volume of trabecular meshwork cells, decreasing the cell volume of Schlemm’s canal and relaxing cells in the canalicular outflow system. Levels of vasoconstrictor molecules such as ET-1 were also found to increase in serum in relation to BMI. ET-1 affects directly and through reduced ocular blood flow causes degeneration of retinal ganglion cells (RGCs) which causes increased IOP. Furthermore, ET-1-induced vasoconstriction results in decreased ocular blood flow affecting RGCs.

In addition, Koçak et al also reported that in patients with obesity class III or with BMI >40 with normal IOP, a decrease in RGC and retinal nerve fibre layer thickness was found and has been associated with optic nerve damage that could lead to normotension glaucoma. As for Newman-Casey et al, obese patients with hyperleptinemia...
In the study by Teberik et al., it was also found that the thickness of the retinal nerve fibre layer was significantly reduced in the obese group compared with the control group (72.7±13.6 mm vs 85.05±52.6 mm; p=0.024), which manifested as RGC damage induced by oxidative stress expression in obese patients that could lead to damage of optic nerves.

In addition, central corneal thickness (CCT) was also found to be increased in obese patients. Based on a study of Su et al., CCT was obtained from 3239 individuals. CCT was found greater in individuals with higher BMI (p=0.038), greater IOP (p<0.001), greater axial length (p=0.005) and greater radius of corneal curvature (p<0.001). Based on the results of this research, CCT was found to be associated with higher IOP as well as higher BMI.

In summary, the relationship between excess body weight as a risk factor for increased IOP values has the following mechanisms: (1) mechanical theory in the form of increased episcleral venous pressure, intraorbital adipose and blood viscosity resulting in an increase in IOP; (2) vascular theory in the form of vascular endothelial dysfunction and autonomic dysfunction resulting in increased IOP (figure 3).

However, one recent study also found a significant correlation between underweight patients who are more susceptible to primary open-angle glaucoma (POAG). Na et al found that compared with normal weight patients (BMI 18.5–23 kg/m²), the risk ratio of POAG increased by 12.9% in underweight patients; however, when compared with obese patients, it was only found to be increased by 3.4%, 6.0% and 8.0% for obese patient class I, class II and class III, respectively. Therefore, people who have more or less body weight are at risk of open-angle glaucoma. One explanation for the effect of underweight is adipose tissue depletion, which has the effect of increasing levels of adiponectin and adipocyte-derived factor. It is said that lower adiponectin levels in individuals who are obese or in individuals who are underweight can increase the risk of atrial fibrillation (AF). AF is a condition with an irregular and rapid heart rate which can cause poor systemic blood flow, one of which is associated with an impact on episcleral venous blood flow leading to an increase in IOP. Therefore, BMI has been shown to have a U-shaped relationship with the risk of AF.

In addition, a potential factor is reduced muscle mass and arterial stiffness. Arterial stiffness increases as muscle mass reduces and ageing happens. Previous studies have shown that increased arterial stiffness has an association with glaucoma and may contribute to the pathogenesis of glaucoma. Low muscle mass, which is affected by a low BMI, may be significantly associated with arterial stiffness and glaucoma.

The strength of this study is that it not only presents the statistical results of the latest meta-analysis on the effect of excess body weight on IOP but also presents a comprehensive theory about several mechanisms that cause excess body weight from mechanical and vascular aspects. However, the limitation of this study is that it only focuses on the effect of excess body weight on IOP. Although we have eliminated several factors that can influence IOP, such as several systemic diseases, we realise that many other factors influence IOP and have not been identified in this study, such as CCT, OPA, RAT, inflammatory cytokines and genetic factors. The second limitation is that each study does not have a standardised classification related to BMI; this is partly because some studies come from Asia and Europe, so the BMI classification used is different. In addition, the tools used to measure IOP in this study are varied and not standardised, so it is possible that there will be differences in IOP measurement results between studies.

Furthermore, further studies are needed to assess obesity as a direct risk factor for glaucoma. In addition, studies on the relationship between low body weight and IOP should also be carried out to complete a comprehensive understanding of the relationship between BMI and IOP. The relationship between underweight and glaucoma in other studies has not been widely studied, and the population-based study by Na et al is the first study to independently evaluate the effect of underweight on the risk of developing POAG.

CONCLUSION

Based on the synthesis of this systematic review, it is concluded that excessive body weight tends to lead to higher IOP, which is a major risk factor for glaucoma.
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REFERENCES
14. Viswanathan M, Ansari MT, Berkman NO, et al. Assessing the risk of bias of individual studies in systematic reviews of health care interventions | effective health care (EHC) program. Effective Health Care (EHC) Program;
### Supplementary table 1. Quality Assessment using Adapted Newcastle-Ottawa Scale (NOS)

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