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Obesity, Blood Pressure, and Intraocular Pressure: A Cross-Sectional Study in Italian Children

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Keywords

Blood pressure \cdot Childhood obesity \cdot Intraocular pressure \cdot Overweight \cdot Refractive error \cdot Myopia

Abstract

Introduction: Several studies in the adult population have shown that obesity is an independent risk factor for elevated intraocular pressure (IOP), whereas data in the paediatric population are sparse and controversial. The purpose of the present study is to investigate the relationship between body mass index (BMI), blood pressure (BP), and IOP in healthy school children. Methods: The survey was conducted among a random sample of 8-year-old Italian students. Data were collected on their health status and behaviours related to obesity (physical activity, food and drinking habits, etc.). Physical examinations, conducted at school, included measurements of height, weight, BP, and IOP. Results: Five hundred and seventy-six subjects were recruited (92.8% response rate); 42.4% were overweight or obese, 58.9% consumed inadequate daily servings of fruit and vegetables, and 87.5% were involved in sedentary activities. Elevated BP/hypertension (HTN) affected 3.6% and high IOP was revealed in 12.5% of the children. In the multivariate analysis, elevated BP/HTN was the only significant determinant of ocular HTN (OR 5.36, 95% CI 1.95–14.73, p = 0.001). **Conclusions:** Our re-

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Introduction

It is well established that a high body mass index (BMI) has become a serious problem affecting about 30% of school-aged children and adolescents [1–3]. The most alarming data refer to the global increase in the prevalence of overweight and obesity observed in the past 3 decades among children and adolescents aged 5–19 years [4].

A number of studies, mostly carried out in the adult population, have also shown that obesity is an independent risk factor for elevated intraocular pressure (IOP) [5, 6], whereas data in the paediatric population are sparse and controversial [7–11]. Elevated IOP might lead to glaucoma, characterized by an irreversible damage of the optic nerve with a gradual impairment of vision. If glaucoma is not treated, sight failure may proceed until the occurrence of complete sight loss. Analogously, elevated blood pressure (BP) is considered as a potential risk factor for IOP in the adult population [6, 12, 13] and it is well

Correspondence to: Claudia Pileggi, claudiapileggi@unicz.it known that overweight and obesity are associated with elevated BP and hypertension (HTN) both in the adult population [14, 15] and among children and adolescents [1, 16, 17].

Early detection of glaucomatous optic nerve damage allows the successful management of its development and elevated IOP is the only modifiable risk factor [18]. Therefore, a positive correlation between BMI, BP, and IOP could indicate obesity control in children also as a crucial strategy for glaucoma prevention. The purpose of the present study is to investigate the relationship between BMI, BP, and IOP in healthy school-aged children.

Materials and Methods

The study population consisted of a random sample of 8-yearold students attending 20 randomly selected primary schools among the 38 primary schools in the geographic area of Catanzaro (Italy) [19]. All parents of sampled children provided written informed consent and completed a questionnaire about their sociodemographic characteristics, anthropometric measures (height, weight), occurrence of chronic diseases, and smoking habits. They also provided data on the health status of their child (occurrence of diseases, eventual ophthalmic surgical interventions, steroid therapy). Before the examination, all children were interviewed about their health behaviours related to obesity, such as physical activity, diet, drinking, time spent watching TV and playing videogames or using computer. The frequency of sports activities and food habits were investigated according to the national nutritional surveillance system, coordinated by the National Institute of Health [20] and involved in the WHO European Childhood Obesity Surveillance Initiative (COSI). Countries participating in COSI explore trends in overweight and obesity among primary school children aged 6-9 years through biannual cross-sectional surveys in order to understand the progress of the epidemic in this population group, gain intercountry comparisons within the European region, and inform action to reverse the trend [3].

Examinations were conducted at school by trained and calibrated examiners. The height and weight of subjects with bare feet were recorded, waist circumference was measured at the umbilicus level over the T-shirt, and BMI was calculated by dividing the weight (in kg) by the square of the height (in m). Subjects were categorized as "at risk of overweight" if their BMI was between the 85th and 94th percentiles, and "obese" if their BMI was equal or over the 95th percentile, in accordance with the WHO [21] and the Italian reference data [22, 23]. In particular, national BMI reference data, developed for subjects aged 2–20 years by the Italian Paediatrics Society of Diabetology and Endocrinology (SIEDP), were used [22, 23]. These tables provide the percentiles of growth not only in relation to age and sex, but also to geographic area. Percentiles for Southern Italy were used.

BP was measured with the subject at rest and in a sitting position, using a mercury sphygmomanometer with an appropriately sized cuff. Three measurements were taken 5 min apart and the average value was used in the analysis for systolic BP (SBP) and diastolic BP (DBP). Normal BP was defined as SBP and DBP <90th percentile for age, sex, and height; elevated BP/HTN was defined as the average SBP or DBP \geq 90th percentile [24–26].

An ophthalmologic examination was performed by an ophthalmologist. IOP was measured by an Icare portable tonometer [27]. Three measurements were obtained and an average value, expressed in mm Hg, was calculated. The results were categorized as "normal" or "high" IOP using the tables of the cross-sectional study conducted by Dusek et al. [8].

Statistical Analysis

The statistical analysis was conducted using the STATA software program, version 14.1 (StataCorp, College Station, TX, USA). Data are summarized using frequencies and percentages for categorical data and mean and SDs for continuous data.

Two models were developed using multivariate logistic regression analyses to identify the variables that affected the following outcomes: elevated BP/HTN (0 = no, 1 = yes; Model 1) and high IOP (0 = no, 1 = yes; Model 2). The following variables were included in the first model: BMI (0 = normal, 1 = overweight orobese), steroid therapy (0 = no, 1 = yes), physical activity (inadequate = never, moderate = 1-3 days/week, adequate ≥ 4 days/ week), consumption of snacks (adequate ≤ 1 serving/week, inadequate ≥ 1 servings/week), daily servings of fruit and vegetable (inadequate <5 daily servings, adequate ≥ 5 daily servings), consumption of soft drinks/fruit juices (adequate ≤ 1 serving/week, inadequate > 1 servings/week), and having had breakfast on the day of examination (0 = no, 1 = yes). In Model 2 the following variables were included: elevated BP/HTN (0 = no, 1 = yes), steroid therapy (0 = no, 1 = yes), time spent on homework $(0 = \le 2 h/day, 1 = >2)$ h/day), and refractive errors (5 categories: 0 = none, 1 = myopia, 2 = hyperopia, 3 = astigmatism, 4 = more than 1 refractive error associated) included as a dummy variable, with no refractive errors being the reference category.

We did not include age and sex in the models because the tables of percentiles used to categorize children in relation to obesity, HTN, and high IOP were already corrected for age and sex. We followed the model-building procedure proposed by Hosmer and Lemeshow [28]. We first performed univariate analysis using the appropriate test statistic, and only the variables with a *p* value ≤ 0.25 were retained in the adjusted model. A backward elimination procedure was applied by setting *p* = 0.4 as the significance level for dropping variables from the models. Adjusted odds ratios (OR) and 95% CIs were calculated.

Results

A total of 576 subjects were recruited, with a response rate of 92.8%. Among them, 551 children underwent a complete physical examination and their main characteristics are reported in Table 1. Students were evenly distributed among males and females; 42.4% were overweight or obese, with a higher prevalence in males (48.5%) than females (35.9%). Moreover, 52% of parents were overweight and 22% obese; 17.4% of children suffered from any chronic diseases, and, of these, 64% suffered from atopy. Nearly half (46.4%) of the surveyed children had undergone steroid therapy in the previous year and, of these, only 9.2% had taken steroid drugs for more than 1 month.

Regarding lifestyle habits, 58.9% consumed inadequate daily servings of fruit and vegetables; just 7.8% and 13.1% did not exceed the daily consumption of snacks and of soft drinks/fruit juices, respectively; 89.1% had had breakfast on the day of the examination; 87.5% of the children spent more than 1 h watching TV or using a computer and playing videogames (data not shown). The mean SBP was 93.7 mm Hg, whereas the mean DBP was 46.4 mm Hg; 0.9% of subjects had elevated BP, and 2.7% HTN. Results of the univariate analysis indicated that elevated BP/HTN in children was significantly associated with overweight and obesity ($\chi^2 = 8.99$, 1 df, p = 0.003), no consumption of breakfast on the day of examination ($\chi^2 = 8.32$, 1 df, p = 0.004), and with steroid therapy ($\chi^2 =$ 3.96, 1 df, p = 0.046; Table 2).

Ophthalmologic examination results revealed that more than half of the surveyed children were affected by a refractive error. Hyperopia was the most common refractive error with a prevalence of 30%. In 12.2% of children visual disorders were uncorrected because they were unknown to the parents (Table 1). Gender did not affect the prevalence of refractive errors ($\chi^2 = 13.55$, 11 df, p =0.259). The mean IOP was equal to 16.5 mm Hg (SD ± 2.9), and high IOP in at least one eye was revealed in 12.5% of the children. No significant difference was found in the IOP between the 2 eyes (*t* test = -0.96, 550 df, *p* = 0.339), whereas a high IOP was significantly more likely in children with elevated BP/HTN ($\chi^2 = 15.72$, 1 df, p <0.001; Table 2). The relationship between BMI and BP is displayed in Figure 1, and that between BP and IOP is shown in Figure 2. Results of the multivariate analysis indicated that elevated BP/HTN was significantly more frequent in overweight and obese children (OR 4.26, 95% CI 1.35–13.42, p = 0.013) and in children who had not had breakfast on the day of examination (OR 0.30, 95% CI 0.10-0.86, p = 0.026; Model 1 in Table 2), and elevated BP/HTN was the only significant determinant of ocular HTN in the children (OR 5.36, 95% CI 1.95–14.73, *p* = 0.001; Model 2 in Table 2).

Discussion

According to current knowledge, childhood overweight and obesity are established risk factors for cardiovascular diseases and, in particular, of HTN. The important new insights added by our study, from a cross**Table 1.** Selected characteristics of the study population (n = 576)

Age, years	8.1±0.5
HTN in parents	
No	434 (79.5)
Yes	112 (20.5)
Ophthalmic diseases in parents	
No	272 (49.8)
Yes	274 (50.2)
Parents' BMI	
Low/normal weight	135 (26.1)
Overweight	269 (51.9)
Obese	114 (22)
Chronic diseases in child ^a	
No	464 (82.6)
Yes	98 (17.4)
Ophthalmic diseases in child ^a	
No	242 (43.9)
Yes, already known	242 (43.9)
Yes, not already known	67 (12.2)
Ophthalmic surgery in child ^a	
No	557 (99.1)
Yes	5 (0.9)
Steroid therapy in the last year	
No	301 (53.6)
Yes	261 (46.4)
Route of administration ^b	
Oral	207 (79.3)
Local (cutaneous, conjunctival, aerosol)	88 (33.7)
Intravenous injection	5 (1.9)
Intramuscolar injection	1(0.4)
SBP, mm Hg ^a	93.7±7.2
<90th percentile – normal BP	542 (97.5)
90–94th percentile – elevated BP	5 (0.9)
≥95th percentile – HTN	9 (1.6)
DBP, mm Hg ^a	46.4±9.7
<90th percentile – normal BP	540 (97.1)
90–94th percentile – elevated BP	2 (0.4)
≥95th percentile – HTN	14 (2.5)
BP ^a	11(=10)
<90th percentile – normal BP	536 (96.4)
90–94th percentile – elevated BP	5 (0.9)
≥95th percentile – HTN	15 (2.7)
BMI ^a	18.7±3.7
<85th percentile – low/normal weight	320 (57.6)
85–94th percentile – overweight	167 (30)
≥95th percentile – obese	69 (12.4)
Ocular HTN ^a	09 (12.4)
No	507 (02)
Yes	507 (92)
103	44 (8)

Data are presented as the mean \pm SD or *n* (%).

^a The numbers that do not add to 576 are due to missing data for the variable.

^b Percentages do not add up to 100 due to multiple responses.

Table 2. Results of the univariate and n	nultivariate analysis
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Variable	Univariate analysis, <i>n</i> (%)	Multivariate analysis		
		OR	95% CI	<i>p</i> value
Model 1. Outcome: elevated BP/HTN		log-likelihood = -67.877, χ^2 = 21.19, <i>p</i> value = 0.0007, number of obs. = 527		
BMI		1		
Low/normal weight	5 (1.6)	1.00 ^a		
Overweight or obese	15 (6.3)	4.26	1.35-13.42	0.013
	χ^2 = 8.99, 1 df, <i>p</i> = 0.003			
Steroid therapy				
No	6 (2.1)	1.00 ^a		
Yes	13 (5.2)	2.26	0.81-6.30	0.117
	$\chi^2 = 3.96, 1 \text{ df}, p = 0.046$			
Daily servings of fruit and vegetables				
Inadequate	14 (4.4)	1.00 ^a		
Adequate	5 (2.2)	0.51	0.17-1.52	0.231
Thequare	$\chi^2 = 1.84, 1 \text{ df}, p = 0.175$	0101	011/ 1102	0.201
Having had breakfast on the day of examination	$\lambda = 1.01, 1.01, p = 0.175$			
No	6 (10)	1.00 ^a		
			0 10 0 96	0.026
Yes	13(2.7)	0.30	0.10-0.86	0.026
	$\chi^2 = 8.32, 1 \text{ df}, p = 0.004$			
Consumption of snacks	15 (2)	1.003		
Inadequate	15 (3)	1.00^{a}		
Adequate	4 (9.5)	0.36	0.10-1.25	0.109
Consumption of soft drinks/fruit juices				
Adequate	3 (4.1)			
	16 (3.4)			
Inadequate		D 1	1.1	
	$\chi^2 = 0.08$, 1df, $p = 0.771$	Backwar	d elimination	
Physical activity				
Inadequate	3 (2.33)			
Moderate	16 (4.5)			
Adequate	- (-)			
	$\chi^2 = 3.38, 2df, p = 0.184$	Backwar	d elimination	
Model 2. Outcome: high IOP		log-likelihood = 13.231, χ^2 = 0.01, <i>p</i> value <0.0001, number of obs. = 534		
6				
Elevated BP/HTN		_		
No	61 (11.5)	1.00 ^a		
Yes	8 (42.1)	5.36	1.95-14.73	0.001
	$\chi^2 = 15.72, 1 \text{ df}, p < 0.001$			
Time spent on homework				
$\leq 2 \text{ h/day}$	33 (10.8)	1.00 ^a		
>2 h/day	32 (14.1)	1.32	0.77-2.24	0.301
~ = 11/ uuy	$\chi^2 = 1.36, 1 \text{ df}, p = 0.242$	1.34	0.77 2.27	0.501
Steroid therapy	$\lambda = 1.50, 1 \text{ di}, p = 0.242$			
Steroid therapy No	29 (12 1)	1.00 ^a		
	38 (13.1)		0 57 1 12	0 221
Yes	31(12.6)	0.81	0.57-1.13	0.221
	$\chi^2 = 0.03, 1 \text{ df}, p = 0.861$			
Refractive errors				
None	28 (11.6)	1.00^{a}		
Hyperopia	31 (14.4)	1.28	0.75-2.18	0.359
Myopia	4 (14.8)	Backward elimination		
Astigmatism	1 (7.1)	Backward elimination		
More than one refractive error			d elimination	
	$\chi^2 = 1.76, 4 df, p = 0.780$			

Bold p values are statistically significant. $^{\rm a}$ Reference category.

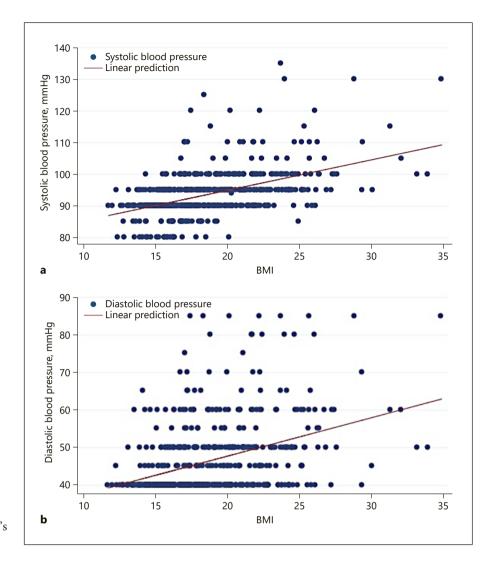


Fig. 1. Relationship between children's BMI and SBP (**a**) and DBP (**b**).

sectional point of view and after adjustment for many factors influencing body weight, is that elevated BP/ HTN related to high BMI in healthy children aged 8 years is consistently associated with high IOP, suggesting that the role of overweight and obesity is mediated through BP increase. Among the few studies that have investigated these associations in children, controversial results have been reported [7-11] and several pathophysiological structural and functional mechanisms linking elevated BP/HTN with high IOP have been proposed. When BMI increases, levels of nitric oxide (NO), one of the principal endothelial-derived vascular relaxing factors, decline with a dysregulation of arteriolar diameters. Reduction of NO induces arteriolar vasoconstriction (Bayliss effect), which increases peripheral vascular resistance, thereby elevating BP. Additionally, microvascular endothelial function has been found to be

inversely correlated with the percentage of body fat in pre-pubertal obese children [29], indicating the deleterious role of fat-induced inflammation on endothelial function that occurs early in life in obese children. In this context the results of a recent meta-analysis that investigated the association of obesity and elevated BP with retinal vessel diameters in children assume a particular interest [30]. Alterations of retinal vessel diameters are considered an effective indicator of cardiovascular risk [31] and the meta-analysis showed that obesity and elevated BP were consistently associated with narrower retinal arterioles. Therefore, it is possible to hypothesize that elevated BP in high IOP children induces a vasoconstrictive response resulting in narrower arteriolar diameters, thus suggesting the opportunity to also investigate the role of high IOP as an indicator of cardiovascular risk in obese children.

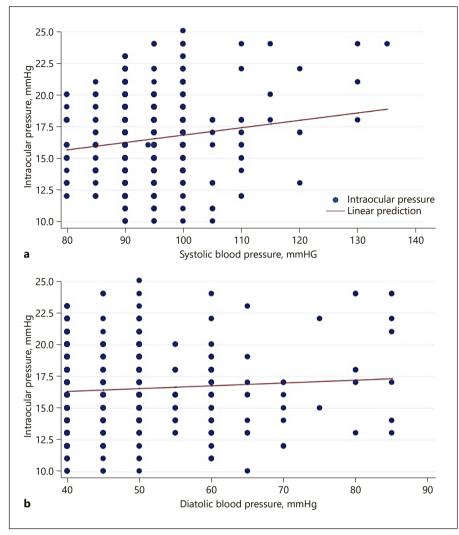


Fig. 2. Relationship between IOP and SBP (**a**) and DBP (**b**).

Another main finding of our study was the high prevalence (12.5%) of IOP in the enrolled children, which is slightly higher than that reported in a previous investigation that evaluated the relationship between IOP and obesity in children (9.7%) [7]. However, as mentioned above, few studies have investigated IOP in children, while research has been mainly focused on the adult population, albeit with contrasting findings [4-6]. Studies performed in children were designed and conducted with varying methodologies with regard to children's eye diseases, mainly conducted in patients with suspected pediatric glaucoma [32], or in hospitalized children who had undergone ocular surgery [33]. Among studies performed in the healthy population, the role of BP was erratically recognized. Indeed, Albuquerque et al. [9] and Koçak et al. [34] did not report any correlation between BMI and IOP; however, although Albuquerque et al. [9] measured

BP in children, they did not include it in the models performed to analyze the possible determinants of elevated IOP, and Koçak et al. [34] did not measure BP in the enrolled children. In line with our results, studies that considered BP as a determinant of IOP [7, 10] showed a positive association between BP and IOP.

Regarding the measurement of IOP, definitions of high IOP varied substantially across studies making it very difficult to compare the different results, reflecting our current poor understanding of what the most effective measurement scheme is. It is necessary, therefore, to take into account the age-specific value of each child, and the use of the percentile curves appeared to us to be the most appropriate tool to achieve this aim.

In our study we also reported that more than half of the surveyed children were affected by a refractive error. A broad range of studies [35–37] have investigated the

association between high IOP and refractive errors, particularly myopia, reporting that the incidence of myopia in patients with IOP was significantly higher than that in the general population. Moreover, the hypothesis that the relationship between glaucoma and myopia could be mediated by BP has been suggested [37]. A prospective study indicated that a high IOP follows the onset of myopia and cannot cause myopia [38], which would imply that myopic eyes have a peculiar mechanism causing high IOP. On the other hand, IOP has been hypothesized to be implicated in the initiation and development of myopia. Elevated IOP could result in myopic axial elongation and promote myopia development. Several studies [39, 40] reported conflicting results that no difference of IOP was identified between myopes and emmetropes. Therefore, the role of IOP on axial length and refractive error development remains controversial.

Limitations

The potential limitations of the study should be mentioned. First, we did not assess the retinal vascular caliber that, over the last decades, has been used as a non-invasive diagnostic tool for the evaluation of cardiovascular health [31]; therefore, no eventual relative association with high BP and IOP could be evaluated. Second, we did not assess the central corneal thickness which could have influenced the IOP measurement. Moreover, previous studies highlighted the association between high IOP and higher BP both in statistical analysis models including central corneal thickness and in those that excluded it [27, 41, 42]. Third, the "gold standard" for IOP measurements is the Goldmann applanation tonometry (GAT), whereas in our study an Icare tonometry was used that, in a significant percentage of children, overestimates IOP by almost 2.3 mm Hg compared with GAT [27]. However, the Icare tonometer has been demonstrated to be reproducible in healthy school children, easy to use, and comfortable for the patients [43, 44]. Therefore, from a public health perspective, the Icare may be useful as a very sensitive screening tool for a first assessment of IOP, to be corroborated by clinical findings and subsequent confirmation by a different tonometry methodology. Finally, information on the metabolic health of the children (lipid profile, insulin resistance, glycemia, etc.) was not collected, though the association of obesity with HTN is also driven by metabolic changes. Our choice was, however, related to the need for the collection of a blood sample, and since the study was on healthy children, it would have been difficult to gain the consent for blood sampling, which is perceived as an invasive procedure. Further research on this

topic should also include these characteristics to investigate in greater depth the role of the metabolic profile of children in the association of obesity with BP and IOP.

Conclusion

High IOP was found to affect 12.5% of 8-year-old school children and appears to be associated with high BP related to high BMI. Therefore, considering that overweight and obesity, elevated BP/HTN, and unhealthy food habits were broadly spread in our population, our results strongly suggest that public health strategies, focused on promoting healthy lifestyles, should include regular IOP evaluation to identify ocular microvascular damage early in children with a high BMI, prior to the development of retinal damage. Further research is needed on the relationship between systemic and ocular biometric factors in the paediatric population, in which early intervention may be extraordinarily effective in the prevention of cardiovascular and ophthalmologic diseases later in life.

Statement of Ethics

Approval from the Institutional Ethics Committee ("Mater Domini" Hospital of Catanzaro, Italy) was obtained (No. 5, 13/3/2015). All parents of sampled children provided written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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There are no funding sources to declare.

Author Contributions

C.P. and M.P. conceived the study. C.P. contributed to data analysis and its interpretation, and contributed to the writing of the first draft of the article. R.P. contributed to the data interpretation and wrote the first draft of the article. C.D.S. and C.G.A.N. collected the data, and contributed to the writing of the first draft of the article. M.P. was responsible for the data analysis and interpretation, and wrote the final draft of the article. C.P. and M.P. critically reviewed the article for important intellectual content and are guarantors for the study. All authors read and approved the final version of the manuscript for submission.

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