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台灣尿液篩檢陽性之高血壓兒童及青少年追蹤研究

A Follow-up Study on Hypertensive Children and Adolescents among Childhood Urine Screening Positives in Taiwan

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台灣尿液篩檢陽性之高血壓兒童及青少年追蹤研究

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本論文係　廖建彰　君 (D94844001)在國立台灣大學環境衛生研究所完成之博士學位論文，於民國 98 年 5 月 6 日承下列考試委員審查通過及口試及格，特此證明

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We, the undersigned, herby recommend that the dissertation entitled, A Follow-up Study on Hypertensive Children and Adolescents among Childhood Urine Screening Positives in Taiwan, submitted by Chien-Chang Liao, be accepted as fulfilling the dissertation requirements for the degree of Doctor of Philosophy

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中文摘要

高血壓是常見的慢性疾病之一，也是心血管疾病的重要危險因子。隨著兒童與青少年肥胖盛行率的增加，青少年高血壓也有增加的趨勢。若能在兒童或青少年時期就發現高血壓，早期控制，有助於預防或改善成年高血壓，防制心血管疾病。目前台灣學童例行身體檢查並未包括血壓量測，相關的本土兒童與青少年高血壓研究也不多。本研究為了探討兒童與青少年高血壓的相關因子，並透過追蹤少年高血壓來探討兒童及青少年高血壓的後續發展，特別是衍生心血管疾病或代謝異常危險。

本研究利用 1992-2000 年的台灣省中小學生尿液篩檢陽性(包括尿蛋白、尿糖及血尿)資料，包括人體量測學檢查、血壓量測及血液生化分析等資料探討中小學生高血壓的特徵和危險因子，進而取樣做追蹤研究。本研究因之分為兩部分：(1)利用這些尿液篩檢陽性學生的基線資料，依照美國國家高血壓教育工作小組標準分類，找出高血壓病例組(N=17548)，再以年級和性別的頻數配對方式，自無高血壓的學生中隨機抽取對照組(N=17548)，進行巢式病例對照研究。(2)邀請居住在台北及台中地區的尿液篩檢陽性學生來醫院做追蹤檢查，包括人體學量測、血壓、血液檢查、尿液檢查及動脈硬化檢查等，將過去學生時期有高血壓的學生視為暴露組(N=347)，無高血壓的學生做為非暴露組(N=641)，進行前瞻性追蹤研究。

結果顯示：(1)病例組的肥胖盛行率約為對照組的 3 倍(17.9% vs. 6.1%, p <0.0001)。在多變項羅吉斯迴歸中，肥胖與高血壓危險有最強的相關(OR = 3.45，95% CI = 3.20-3.72)，其次是膽固醇過高，兩者與高血壓都有劑量效應的關係(p<0.0001)。高血壓危險比與出生體重呈現 V-型關係。非肥胖學生中，相較於出生體重正常學生，低出生體重(OR=1.10，95% CI=0.96-1.27)與高出生體重(OR=1.19，95% CI=1.05-1.34)都有較高的高血壓危險比。相較於有最低 IgA 10 位數的學生，最高 IgA 10 分位數的學生有較高的高血壓(OR = 1.20，95% CI = 1.08-1.34)、高膽固醇(OR = 1.22, 95% CI = 1.11-1.34)及空腹血糖異常危險比

(OR=1.77，95% CI = 1.62-1.93)。最高 10 分位數的肥胖學生的空腹血糖異常危險比增加到 2.93 (95% CI = 1.93-4.44)。(2)在追蹤研究中發現，相較於中小學時無高血壓的人，有高血壓的人在成年後仍有較高的高血壓危險(OR=4.19，95% CI=2.42-7.28)，空腹血糖異常(OR=4.70，95% CI=1.62-13.6)及代謝症候群(OR=4.20，95% CI=1.23-14.3)的危險也較高。

本研究顯示肥胖是兒童與青少年高血壓的主要危險因子，出生體重與 IgA 也與兒童及青少年高血壓有關。有高血壓的兒童及青少年在成年後較有心血管代謝的健康問題。

關鍵字：高血壓、兒童及青少年、肥胖、出生體重、免疫球蛋白 A、追蹤、心血管代謝異常

Abstract

Hypertension is one of common chronic diseases and an important risk factor of cardiovascular disease. With the increasing prevalence of childhood obesity, the childhood hypertension is increasing as well. Early detection and control of hypertension for children and adolescent may help to prevent the adulthood hypertension and other cardiovascular diseases. Blood pressure measurement is not included in the regular health checkup for school children and there are limited studies on hypertension in children and adolescents. This study is to investigate factors associated with childhood hypertension using data obtained from a mass urine screening campaign among school children in Taiwan Province, 1992-2000. We also conducted a follow-up study among children with hypertension to investigate the impact of childhood hypertension on the early adulthood health, 10 years after the screening campaign, especially the cardiovascular metabolic abnormalities.

This study therefore consists of two projects: (1) The first study is a case-control study. We identified school children with urine screening positive in the 1992-2000 campaign. We used the childhood hypertension criteria of American National High Blood Pressure Education Program Working Group to determine hypertensive cases. The available information included anthropometrics, measurement of blood pressure, and selected biochemicals. We selected non-hypertensive children also from urine screening positive children as controls, frequency matched by age and sex to conduct nested case-control analyses for risks associated with childhood hypertension. (2) The second part of study is a follow-up study. Urine screening positive students who lived in Taipei and Taichung were invited for a follow-up health examination including questionnaire interviews, anthropometric measures and blood pressure, blood tests, urine screenings, and exams of atherosclerosis. In this prospective cohort study, we considered those hypertensive children identified from the mass urine screening

campaign as exposed group and non-hypertensive students as non-exposed controls for comparison.

In the case-control study we found: (1) The prevalence of obesity in cases was three times higher than that in controls (17.9% vs. 6.1%, p <0.0001). The multivariate logistic regression showed that the strongest risk for childhood hypertension was associated with obesity (OR = 3.45, 95% CI = 3.20-3.72). High cholesterol was also a factor associated with childhood hypertension. Both factors had the dose-response relationship with hypertension (p <0.0001). (2) A V-shape relationship was found between birth weight and hypertension risk. Among non-obese children, those with higher birth weight (OR = 1.19, 95% CI = 1.05-1.34) or low birth weight (OR = 1.1, 95% CI = 0.96-1.27) had higher risk of hypertension compared with children with the weight of 2500-2999 gram. (3)Compared with children with the lowest IgA decile, children with the highest IgA decile had higher risks for hypertension (OR = 1.20, 95% CI = 1.08-1.34), hypercholesterol (OR = 1.22, 95% CI = 1.11-1.34), and impaired fasting glucose (OR = 1.77, 95% CI = 1.62-1.93). The risk of impaired fasting glucose increased to 2.93 (95% CI = 1.93-4.44) among obese children with the highest decile of IgA.

In the follow-up study, those with childhood hypertension at the baseline remained at a high risk of hypertensive than children without childhood hypertension (OR = 4.19, 95% CI = 2.42-7.28). They were also at higher risks of impaired fasting glucose (OR = 4.70, 95% CI = 1.62-13.6), and developing metabolic syndrome (OR = 4.20, 95% CI = 1.23-14.3).

This study shows that obesity is the significant risk factor of hypertension for children and adolescents. High levels of IgA and birth weight are also associated with childhood hypertension. Childhood hypertension increases the risk of remaining hypertension and developing metabolic abnormalities later in young adulthood.

Key words: Hypertension, Children and adolescents, Obesity, Birth weight, Immunoglobulin A, Follow-up, Cardiovascular metabolic abnormalities

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第一章　緒論

第一節　研究背景與動機

腦中風與心臟病分別位居台灣的第二及第三大死因，2005 年約有 26,109 人因腦中風或心臟病而死亡，而兩者皆與高血壓有很強的相關[1, 2]。高血壓也是糖尿病與腎臟病常見的共病，自 2003 年起高血壓已躍升為國人第十大死因，每年約有 1,800 人因高血壓而死亡，顯示其重要性[1, 2]。因此對於心血管疾病的防制，找出高血壓的危險因子，進而控制高血壓顯得更為重要。

高血壓是台灣的重要健康問題，影響著老年人口，一直被衛生單位視為中老年人疾病防治的主要項目，衛生當局也積極於此。鑑於青少年中風病例逐漸增加，顯示兒科高血壓也不容忽視，需先期預防，並鑑定相關危險因子。

從台灣的生命統計資料來看，兒童及青少年的心血管疾病及其他與高血壓有關的疾病之死亡率有上升的趨勢[1]。過去的研究指出，兒童及青少年時期的高血壓與成年後的高血壓有很強的相關[3, 4]，但兒童及青少年高血壓，較不受醫護人員的重視，時常被低估[5]。若能夠在兒童或青少年時期就發現高血壓，早期控制，可能有助於預防或改善成年高血壓[6, 7]，正因為如此，Rao 等(2007)認為血壓的量測應成為學童例行身體檢查的一部分[8]。目前台灣學童例行身體檢查並未包括血壓量測，相關的本土兒童與青少年高血壓研究也不多[9, 10, 11]，因此少年高血壓的相關因子及其對後來生活健康影響值得做進一步的探討。

財團法人中華民國衛生保健基金會(The Chinese Foundation of Health, CFH)在 1992-2000 年間曾進行台灣省中小學生尿液篩檢，檢測尿蛋白、尿糖和潛血。連續陽性兩次以上的學生，在第三次時進行較詳細的檢查，包括身高、體重等人體量測學檢查、血壓量測及血液生化分析等。本研究利用台灣省中小學學童尿液篩檢資料，依照美國心臟學會兒童與青少年高血壓標準分類分析相關因子[13]，並進行青少年高血壓追蹤，目的在探討兒童及青少年高血壓的危險因子之外，進而觀察青少年高血壓的後續健康是否有改善，以提供疾病預防之參考。

第二節　研究目的

本研究期望了解孩童高血壓的危險因子、共生病及孩童高血壓對後來成年的健康影響。本研究可能達成以下目的：

1. 估計兒童與青少年高血壓的盛行率
2. 探討兒童與青少年高血壓的相關因子及共病
3. 探討出生體重與兒童及青少年高血壓之相關性
4. 探討免疫球蛋白 A 與兒童及青少年高血壓之相關性
5. 評估兒童及青少年高血壓對後來成年的健康影響，特別是心血管代謝異常。

第二章　文獻回顧

第一節　兒童與青少年高血壓的定義及盛行率

有別於成人高血壓的標準(收縮壓 ≥140 mmHg 或舒張壓 ≥90 mmHg)，決定兒童高血壓的標準較為複雜一些。兒童與青少年高血壓的定義是依據年齡、性別及身高來決定[12]。首先於該性別的身高年齡之成長曲線圖上，取得受測者的身高年齡百分比，再將百分比對照美國國家高血壓工作小組(National High Blood Pressure Education Program Working Group, NHBPEPWG)提供的該身高年齡下的標準血壓，找出受測者的血壓，落在標準血壓表的百分位。美國高血壓工作小組針對 1 至 17 歲的孩童，做一個年齡、性別、身高特定的標準。兒童及青少年的收縮壓 ≥95 百分比或舒張壓≥95 百分比者即為高血壓。舉例來說，一位七歲男童身高在整個族群的 75 至 89 百分比，其高血壓的收縮壓標準為 116 mmHg，舒張壓為 77 mmHg，同年齡、身高百分比的女童則為 114 mmHg、75 mmHg[12]。

根據美國高血壓工作小組的建議，針對三歲以上的兒童，應於每次門診時例行監測血壓。小於三歲者，若伴有某些先天性疾病(如：先天性心臟病、器官移植病人、癌症等)，也應做例行性血壓監測。血壓測量方式以聽診為佳，若以其他方式測量到異常血壓時，應再以聽診方式重新測量加以確定[12]。

另外，根據美國心臟學會(American Heart Association)在 1993 年出版的高血壓入門(Hypertension Primer) [13]，兒童及青少年高血壓標準如下：

Table 1-1. Criteria of hypertension in children and adolescents from American Heart Association

Age, years	SBP, mmHg	DBP, mmHg
6-9	≥122	≥78
10-12	≥126	≥82
13-15	≥136	≥86
16-18	≥142	≥92

Source: American Heart Association: Hypertension Primer，1993

相較於美國心臟學會的標準，美國高血壓工作小組的兒童及青少年高血壓標

準雖較複雜，但常被許多研究所採用[3]。Sorof 等人對美國 5,102 位 10-19 歲的兒童及青少年，連續三次做血壓篩檢(three occasional screening)，第一次篩檢高血壓盛行率為 19%，第二次再對有高血壓的學童篩檢(只剩 56%具有高血壓)，盛行率減為 9.5%，而第三次的篩檢，高血壓盛行只剩 4.5% [3]。因此 Sorof 等人建議應用三次的篩選來定義真正的兒童及青少年高血壓。但這樣的方法在實際上執行常會有困難，目前真正用三次篩選來估計兒童與青少年高血壓的研究並不多。

一般來說，高血壓的盛行率會隨著年齡的增加而上升，男性的盛行率也比女性高。兒童高血壓也是如此，但盛行率仍隨著不同的種族而有所變異。Table 1-2 呈現各國的盛行率，印度的兒童高血壓盛行率最低(0.5%) [14]，而巴西有最高的兒童高血壓盛行率(22.0%) [15]；Chu 等研究肥胖學生，發現盛行率高達 17.1% [10]。各國的兒童高血壓盛行率有很明顯的不同[16]，除了因為年齡、性別及種族不同之外，量測血壓的方法及高血壓的標準也是原因之一。

第二節　人口社會地理因子與少年高血壓之關係

年齡與性別是影響血壓的重要因素。在 Ohio 州的 3-18 歲兒童與青少年中，年齡每增加一歲，高血壓的危險比就會增加 9%(95% CI = 3-16%) [5]。在路易斯安那州 5-17 歲小孩中，年齡每增加一歲，收縮壓就會上升 0.2 mmHg (95%可信限 [confidence interval, CI] = 0.1-0.2)；而男孩較女孩有較高的危險比(OR = 1.50，95% CI = 1.15-1.95) [17]。在土耳其的 12-14 歲學童中，年齡每增加一歲的高血壓危險比為 1.14(95% CI = 1.13-1.76) [18]，男孩較女孩有較高的高血壓危險比(OR = 1.92，95% CI = 1.34-2.75)。相較於台北國小一年級女童，男童的高血壓危險比為 1.41 (95% CI = 1.13-1.75) [9]。由此可見年齡與性別對血壓之影響。

文獻顯示，高血壓的盛行率在種族間有明顯的不同。由美國 3 個州的篩檢研究發現，黑人男童的高血壓盛行率為 22.6%，高於白人男童的 17.4%($p < 0.05$)，女童也有相似的結果(10.0%對 4.8%，$p < 0.05$) [19]。在美國印第安那州的 5-19 歲

學童中，黑人血壓平均值高於白人的血壓平均值，包括收縮壓(101.4±10.4 對 98.3±11.2 mmHg，p = 0.0001)及舒張壓(62.9±10.1 對 60.4±10.5 mmHg，p = 0.001) [20]。但另外一項研究卻顯示，在美國 5-17 歲學童中，黑人學童的高血壓危險比(odds ratio, OR)低於白人學童(0.81，95% CI = 0.68-0.96) [21]。

兒童與青少年的家庭社會經濟地位也是高血壓的相關因子。根據一項跨國研究，在俄國，相較於 3-18 歲中階社經地位的學生，低社經地位的學生其高血壓危險比為 1.4 (95% CI = 1.2-1.7)，這樣的危險比在美國學生是 1.3 (95% CI = 1.1-1.6)，但在中國則無顯著差異[22]。低社經地位在剛果的青少年中也是高血壓的危險因子(OR = 1.2，95%CI = 1.1-1.3) [23]。以居住地區來說，中國少年住在都市的較住在鄉村的有較高的高血壓危險(OR = 1.5，95% CI = 1.1-2.0) [22]。印度 11-17 歲學生中，住在都市的學生較住在鄉村的有較高的高血壓盛行率(6.7%對 2.6%，p<0.01) [24]。

第三節　飲食、生活型態及家族病史與少年高血壓

飲食也是血壓的相關因子，尤其是年輕族群 [25-27]。過去的研究認為鈉與鉀的攝食與兒童血壓有關。青少年對咖啡因的攝取會影響血壓[28]，每日咖啡因攝取≥100 mg 的非裔美國青少年其收縮壓高於每日攝取 0-50 mg 的青少年(血壓平均差異 = 6.0 mmHg，p<0.05) [29]。而豐富的蔬菜與水果的攝取有助於改善兒童的血壓。相較於蔬果攝取量較低(<4 份/天))的兒童，蔬果攝取量較高(≥4 份/天)的兒童有較低的收縮壓(107.8±1.8 對 112.0±1.2 mmHg，p < 0.05) [25]。不論是男孩或女孩，相較於攝取葉酸(folate)較高的青少年，葉酸攝取量較低者其平均舒張壓較高(男孩：72 對 67 mmHg，p = 0.002；女孩：76 對 73 mmHg，p < 0.05) [30]。抽菸與喝酒習慣在兒童及青少年的盛行率相對較低，因此少有研究探討少年抽菸與喝酒對高血壓的影響[31]。

有些文獻認為家族高血壓病史對兒童與青少年的血壓也會有影響[32, 33]。有

家族高血壓病史的少年其收縮壓較無家族高血壓病史的少年高(120±1 對 115±2 mmHg，p = 0.009) [32]。土耳其的 12-14 歲學童中，相較於沒有家族高血壓病史的學童，有家族高血壓病史的學童有較高的高血壓危險(OR = 1.96，95% CI = 1.33-2.89) [18]。

第四節　肥胖、高血糖、高血脂與少年高血壓

肥胖是高血壓的重要危險因子之一，對於兒童及青少年的高血壓，肥胖相關更是重要[34-37]，且少年肥胖與成年後的肥胖也有相關[38]，肥胖甚至會影響從青少年至老年的動脈硬化[39]。在伊朗 6-18 歲學童的研究發現，肥胖者較非肥胖者有較高的高血壓危險比(OR = 1.42，95% CI = 1.26-1.68) [34]。路易斯安那州 5-17 歲小孩中，相較於體重正常的小孩，體重過重或肥胖的小孩其收縮高血壓的危險比為 4.5(95% CI = 3.6-5.8)，舒張高血壓的危險比為 2.4 (95% CI = 1.8-3.0) [35]。德州 8-13 歲學童中，相較於體重正常的學童，肥胖或體重過重的學童其高血壓危險比為 3.05(95% CI = 2.11-4.41) [36]。奧克拉荷馬州 4-18 歲體重過重學童的高血壓危險比則為 3.76(95% CI = 2.64-5.37) [37]。休士頓 11-17 歲的學童中，相較於體重正常者，體重過重的學童其高血壓危險比為 4.26(95% CI = 3.12-5.83) [40]。土耳其的 12-14 歲學童中，體重過重學生其高血壓危險比高達 6.40 (95% CI = 4.49-9.12) [18]。與在瑞士 10-15 歲體重正常小孩相較，胖小孩的高血壓危險比更高達 16.2 (95% CI = 9.1-28.9) [41]。如此可見肥胖對兒童高血壓的影響極為重要。

近年來許多已開發國家及部分開發中國家的兒童及青少年肥胖盛行率有逐年增加的情況[8, 42]。1980 年台灣 12-15 歲男童肥胖盛行率為 12.4%，1986 年為 14.8%，到了 1996 增加至 16.4%，女童的盛行率則分別為 10.1%、11.1%以及 12.9%，都有上升的趨勢[43]。而隨著兒童肥胖率的上升，兒童高血壓的盛行率也有逐年增加的趨勢[43]。

以高血壓的盛行率來看，Jago 等人(2006)在美國 3 個州的研究發現，體重過

重的學童高血壓盛行率明顯高於體重正常學童(24.6%對 6.9%，p = 0.02) [19]。在休士頓 12-16 歲的中學生中，肥胖學生較無肥胖者有較高的高血壓盛行率(33%對 11%，p < 0.001) [44]。以色列的一項大型調查(N=560,588)結果顯示，16-19 歲男性青少年肥胖者高血壓前期盛行率為 66.4%，高於體重過重(64.7%)及正常體重(56.5%)的青少年(p < 0.001)；女性青少年的高血壓前期盛行率也是肥胖者(55.6%)高於體重過重(46.9%)及體重正常者(34.3%) (p < 0.001) [45]。

若以血壓平均值來看，西班牙瓦倫西亞市 6-16 歲學童，肥胖者的血壓平均值皆較非肥胖者高，包括收縮壓(112.6±6.6 對 107.8±6.9 mmHg，p < 0.001)及舒張壓(65.9±4.4 對 64.2±4.2 mmHg，p < 0.05) [46]。澳洲 11-16 歲的學生，肥胖者較體重正常者有較高的舒張壓(67±2 對 61±2 mmHg，p = 0.04) [47]。一項本土的資料顯示，台北 12-16 歲的肥胖男孩比非肥胖男孩有較高的收縮壓(121.1±11.8 對 112.8±12.5 mmHg，p < 0.001)與舒張壓(72.8±10.8 對 66.7±8.8 mmHg，p < 0.001)；肥胖女孩的收縮壓(113.5±12.5 對 102.8±11.7 mmHg，p < 0.001)與舒張壓(73.1±10.3 對 66.7±8.8 mmHg，p < 0.001)也較非肥胖女孩高[10]。

反過來看，一項針對捷克的青少年研究發現，有嚴重高血壓的少年比無高血壓的少年，有較高的 BMI (median=24.9 對 22.3 kg/m^2，p = 0.0001) [16]。美國德拉威 2-18 歲學童中[48]，有高血壓男孩的 BMI 平均值高於血壓正常的男孩(36.3±8.3 對 31.7±5.5 kg/m^2，p < 0.001)，有高血壓女孩的 BMI 平均值也較血壓正常的女孩高(36.4±9.3 對 32.1±7.1 kg/m^2，p < 0.001)。

而過去的文獻也報導，肥胖兒童及青少年減重後(-1.7 kg/m^2)，其收縮壓(-3.9 mmHg, p < 0.001)和舒張壓(-4.2 mmHg, p < 0.001)都有明顯的下降[49]。以上證據顯示兒童與青少年肥胖與高血壓之關係密切，由此可見肥胖對少年血壓的影響非常重要，而肥胖少年若減重，其血壓會得到一定的改善。

血糖也是與高血壓相關的一項重要因子，有高血壓的成人常會有高血糖的問題，而有糖尿病的人有會有較高的高血壓危險，在兒童與青少年中也是如此[50]。

過去的本土研究也發現兒童高血壓會增加糖尿病的危險(OR = 1.70，95% CI = 1.07-2.70) [51]。墨西哥 6-13 歲學齡兒童中，收縮壓與空腹血糖之相關係數為 0.124，但不顯著[52]。

血脂肪與兒童高血壓也有相關。美國德拉威 2-18 歲學童中，有高血壓男孩的三酸甘油脂(triglyceride, TG)平均值高於血壓正常的男孩(148.7±77.3 對 115.4±51.2 mg/dL，p = 0.027)，高密度脂蛋白膽固醇(high-density lipoprotein cholesterol, HDL)平均值低於血壓正常的男孩(39.6±12.7 對 45.0±10.0 mg/dL，p = 0.001)，但女孩無此現象[48]。在芬蘭 12 至 18 歲的青少年中，血壓高的男孩相較於血壓低的男孩有較高的低密度脂蛋白膽固醇(Low-density lipoprotein cholesterol, LDL) (3.24±0.68 對 3.01±0.70 mmol/L，p=0.05)及三酸甘油脂(0.87±0.36 對 0.73±0.27 mmol/L，p = 0.003) [53]。一項針對捷克的青少年研究發現，有嚴重高血壓的少年比無高血壓的少年，有較低的 HDL(median = 1.2 對 1.4 mmol/L，p = 0.0001)及較高的三酸甘油脂(median = 1.2 對 1.0 mmol/L，p = 0.0201)，而當 LDL 每增加 0.1 mmol，高血壓的危險比為 1.25 (95% CI = 1.07-1.46) [16]。在荷蘭 15-18 歲的青少年中，相較於沒有高血壓的青少年，有高血壓的青少年有較高的總膽固醇(4.3±0.8 對 3.9±0.6 μmmol/L，p < 0.01)及 LDL(2.4±0.68 對 2.09±0.53 μmmol/L，p < 0.01) [54]。一項針對墨西哥 9-12 的學童研究發現，兒童的收縮壓與三酸甘油脂(r = 0.464，p < 0.001)及總膽固醇(r = 0.291，p < 0.01)有正相關[52]。

另外，過去的研究也發現青少年的血壓與體脂肪百分比有關[55, 56]。在葡萄牙 8-15 歲的學生中，不論是男孩(OR = 1.9，95% CI = 1.3-2.8)或女孩(OR = 2.6，95% CI = 1.8-3.8)，相較於體脂肪百分比較低者，體脂肪百分比較高者其高血壓的危險比較高；有較高的總膽固醇之女童其高血壓危險比也較高(OR = 1.6，95% CI = 1.0-2.4) [56]。

第五節　出生體重、發炎反應與少年高血壓

出生體重是胎兒成長的一項重要指標，影響的不只是兒童與青少年及的健康，也影響著成年後的健康，包括糖尿病及心血管疾病等[34, 57-65]。根據一項在伊朗的研究，出生體重過重(OR = 1.04，95% CI = 1.02-1.64)或過輕(OR = 1.52，95% CI = 1.23-2.49)的學童皆較出生體重正常的學童有較高的高血壓危險比[34]。在美國對 55908 位 7 歲學童的研究顯示，出生體重每增加一公斤，高收縮壓危險比會為 2.2(95% CI = 1.9-2.5)，高舒張壓危險比為 1.8 (95% CI = 1.6-2.1) [65]。但若以相關係數來看，許多研究都認為出生體重與收縮壓或舒張壓並無明顯相關[59, 66]。也有研究指出，肥胖在出生體重與少年血壓之關係中，扮演交互作用的角色，出生體重似乎對於體重正常的少年的影響較明顯[60, 66]。因此不論是出生體重低或出生體重高都會有較高的少年高血壓危險[34, 64, 65]。

發炎反應也被許多研究報導跟代謝症候群有關，而高血壓是代謝症候群中的一項重要因子，但探討發炎反應與兒童高血壓之關係的研究目前仍少[67-70]。High-sensitive C-reactive protein (hsCRP)、白血球計數、IL-6 等都是常見的發炎反應指標，而最近也有研究報導免疫球蛋白 A (immuglobulin A, IgA)之濃度也可視為一項發炎反應指標[67-69]。以 hsCRP 來說，根據西班牙一項針對 6-9 歲孩童的病例對照研究，hsCRP 與血壓有正相關(SBP: r = 0.117，DBP: r = 0.165)，但沒有達到統計上的顯著[71]。以白血球計數來看，在韓國 10-19 歲的少年中，白血球的計數與收縮壓有正相關(r = 0.22，p < 0.05) [72]。

過去的研究曾經報導，相較於沒有糖尿病的人，有第 2 型糖尿病的成人其血中 IgA 濃度較高(Median：2.81 對 1.95 g/L，p < 0.001) [68]。在有高膽固醇血症的成人中，IgA 濃度與膽固醇有顯著的相關(r = 0.59，p < 0.0001) [67]。血中 IgA 濃度會隨著年齡增加而增加[68]，有抽菸或喝酒習慣的人其體內的 IgA 濃度也較高[69]。但目前尚無研究探討兒童與青少年 IgA 濃度與高血壓或其他代謝異常的問題。

第六節　其他與少年高血壓的相關因子

過去也有一些研究報導兒童時期的血中尿酸會影響血壓[73]。在台灣全國性的健康營養調查中，6-12 歲兒童的尿酸與血壓有明顯的相關(收縮壓：$r = 0.207$，$p < 0.001$；舒張壓 $r = 0.102$，$p < 0.001$) [11]。而美國的一個兒童高血壓病例對照研究發現，尿酸與血壓有很強的相關(收縮壓：$r = 0.81$，$p < 0.0001$；舒張壓 $r = 0.66$，$p = 0.001$) [74]。美國全國健康營養調查的青少年中，經校正年齡、性別、種族、CRP、血脂、血糖、腰圍及胰島素後，高尿酸的少年較低尿酸的少年有較高的血壓過高危險(OR = 2.26, 95% CI = 1.03-4.98)，但再經過校正 BMI 後就不顯著(OR = 2.05, 95% CI = 0.94-4.48) [75]。根據著名的 Bogalusa Hear study，從兒童到成年的尿酸改變會增加成年血壓的上升($\beta = 5.85$, $p = 0.025$) [73]。

另外，環境因子也會影響兒童與青少年高血壓 [76]，但相關研究目前並不多。Belojevic 等人曾報導過塞爾維亞 3-7 歲幼稚園學童中，暴露到交通噪音的兒童收縮壓有明顯上升的情況[76]。

第七節　少年高血壓對成年後的健康影響

許多研究發現，孩童時期有高血壓會影響成年後的健康，尤其是心血管代謝問題，甚至是動脈硬化。美國的一個世代研究發現，相較於收縮壓正常的兒童(5-7 歲)，收縮壓過高的兒童在成年後(≥30 歲)有較高的高血壓(OR = 4.5，95% CI = 1.1-17.7)及代謝症候群危險(OR = 3.1，95% CI = 1.0-9.7) [77]。荷蘭的一個世代研究發現，青少年時期的收縮壓與成年後的動脈硬化有顯著相關[78]。芬蘭的一個世代研究經過 21 年的追蹤後發現，青少年時期(12-18 歲)的收縮壓每增加 1mmHg，成年後的頸動脈中皮層厚度會增加 0.013 mm ($p < 0.001$) [79]。少年高血壓對成年後的健康有明顯影響，不容忽視。

第三章　研究方法

第一節 研究設計

(一)基線資料研究

在 1992 年至 2000 年期間，中華衛生保健基金會(Chinese Foundation of Health, CFH)與台灣省政府衛生處及教育廳贊助合作，為全台灣省(不包括北、高兩市)中小學(包括國民小學、國民中學、高中職)學生進行每學期一次的尿液篩檢；1992 年約有 2,615,000 位學生接受尿液篩檢，1993 至 2000 年每年約有 2,932,000 位學生受檢。目的是要篩檢有尿蛋白(proteinuria)、尿糖(glucosuria)或血尿(hematuria)的學生。

為了避免因為過度運動性蛋白尿產生，成為偽陽性，均採取早晨的第一次尿液。為了採取尿液的正確性，CFH 分發說明書給家長及老師，請其協助採取尿液檢體。CFH 在各縣市均設立篩檢工作站，工作站將器材運送至學校，再由學校老師協助分發給學生，在約定的檢查日，尿液檢體由工作站人員以冷藏車送回檢驗工作站。為了保存尿液檢體，各縣市檢驗工作站除檢驗場所置有冷藏櫃外，亦配置冷藏車，因此由檢體的收集到檢驗的每一個過程，均可保持在冷藏的狀態，以免尿液變質。另外，CFH 在偏遠地區之學生採尿瓶中加入防腐劑，以延長尿液檢體之保存時間。

第一次尿液篩檢異常的學生，會被邀請進行第二次的尿液篩檢，若兩次尿液篩檢皆為異常的學生，則會被邀請接受進一步的身體檢查。衛生局協助 CFH 與轄區的衛生所合作，到各學校進行採血、採尿及身體檢查，身體檢查項目包括理學檢查(包括身高、體重及血壓的量測)、血液檢查(包括總膽固醇、血中尿素氮[blood urea nitrogen, BUN]、肌酸酐[creatinine]、白蛋白(albumin)以及免疫球蛋白A[immunoglobulin A]等)以及第三次尿液檢查。三次陽性學生則轉介給醫師做進一步追蹤或照護。

經過了九年的篩檢，CFH 檢查出有 192,213 位學生尿液篩檢異常且接受身體

檢查，經排除 63,800 筆重複或無身份證號碼紀錄、24,561 位具不合理血壓值學生以及 12 位無年級資料學童，共有 103,840 位學生具有可靠的資料進行三項研究。這三項研究為：(1)高血壓重疊病例對照研究

(2)出生體重與青少年的高血壓相關

(3)兒童與青少年的 IgA 與高血壓、高血糖及高血脂之相關

我們以過去尿液篩檢異常學生的基線資料(baseline data)進行分析。在9年的檢查資料中，先排除無身份證號碼或身份證號碼重複資料。我們檢視其血壓測值，將SBP小於40 mmHg、SBP大於250 mmHg、DBP小於30 mmHg及DBP大於150 mmHg等血壓上下2.5%極端資料排除，再將年級不正確的資料排除，最後有99350名青少年的資料納入研究。我們依照美國高血壓工作小組的兒童及青少年高血壓的標準，篩選出具有高血壓的少年作為病例組，再依照年級與性別做頻率配對(frequency matching)，以隨機的方式抽選與病例組相同數量不具高血壓的對照組，之後進行重疊病例對照研究(nested case-control study)。

過去很多研究報導出生體重與少年高血壓有關，因此在探討少年高血壓時，出生體重值得注意。我們利用本研究的基線資料，串聯了出生登記資料庫，收集了這些尿液篩檢陽性學生的出生資料，再將缺漏出生體重的人排除後，最後共有89668名學生，可以利用這些資料試著探討出生體重、篩檢期間的BMI與少年高血壓之關係。

最近幾年有許多研究探討發炎反應與心血管代謝異常問題，而IgA可視為發炎反應的一種指標。因此我們也利用本研究的基線資料，經排除缺少IgA資料的個案後，最後共有92514名兒童與青少年，可用以探討IgA與少年高血壓、高血糖及高血脂之相關。

(二)追蹤研究

從 103,756 位具有可靠基線資料的尿液篩檢陽性學生中，依照美國心臟學會的兒童血壓標準加以修改(修改為 16-18 歲：收縮壓≥140 mmHg，舒張壓≥90

mmHg)，篩選出 9,227 位(5.6%)具有高血壓的學生，再將姓名、地址或電話資料不全的學生排除，最後滿足條件的高血壓學生有 5753 位，而其中居住在台北縣的 1,251 位及台中市的 205 位學生為本計畫高血壓暴露組的追蹤對象。在 103,756 位學生中，有 94529 位不具高血壓，其中住在台北縣的 17448 位及台中市的 3055 位學生為本研究高血壓非暴露組的追蹤對象(Figure 1-1)。

以暴露組追蹤方式來說，首先我們將少年高血壓追蹤檢查的邀請函依照學生資料上的地址寄出，在邀請函寄出三天後，經過訓練的研究助理及臨時工依照資料上的電話號碼撥打，以確認學生或其家長是否收到邀請函。若學生沒收到邀請函，我們經過詢問學生或其父母正確地址後補寄邀請函，同時並進行少年高血壓追蹤檢查的電話問卷訪問及邀請。受訪者若願意參加少年高血壓追蹤檢查，我們即安排時間進行檢查。青少年接受檢查後的三個星期內，我們以電話與青少年約定時間，請他們回來醫院由醫師向青少年解釋檢驗報告內容，並將報告提供受檢者。本研究的對照組追蹤方式主要以邀請函的寄送為主。因為對照組的人數眾多，受限於研究資源及經費，邀請函依追蹤對象的地址寄出後，不再撥打電話通知。對照組收到邀請函後，部分的學生主動打電話來詢問或預約檢查，經過訓練的研究助理及臨時工利用對照組回電時邀請他們來做追蹤檢查。

我們先以信函向家長說明本計畫的目的和程序及功能等，接著以電話聯絡約定檢查時間。在檢查之前，我們會先向受檢者說明檢查的內容及項目，再請受檢者填寫檢查同意書，之後再進行檢查。少年高血壓追蹤檢查的內容包括：理學檢查(包括身高、體重、腰圍及臀圍等)、生化檢查(空腹血液及尿液)、Dynapulse 血壓量測、頸動脈超音波及 colin 血管彈性等。但受限於研究資源，台中市區的追蹤檢查不包括頸動脈超音波檢查。

第二節 資料收集

少年高血壓追蹤研究的資料收集包括問卷資料、理學檢查、尿液檢查、抽血檢查、

頸動脈超音波檢查及 Colin 血管彈性量測。

(1) 問卷資料

在諮詢專家及兩位心臟科醫師進行各項檢查時，我們同時檢視少年心血管健康問卷。問卷內容包括人口社會經濟狀況資料、居家及工作環境、個人生活習慣、個人疾病史、父母親的生活習慣、父母疾病史及家族疾病史。人口學變項包括性別、年齡、身高、體重、出生體重、2-5 歲的體型、教育程度、職業、婚姻狀態、家庭收入、兄弟姊妹人數及排行以及初經年齡等。居家工作環境包括住家附近是否有工廠、機場、機車行、汽車修配場、平交道、中大型醫院、夜市和大型卡車經過等設施或建築物，以及住所居住年數、是否有噪音暴露、工作年數、是否有化學物質暴露等。個人生活習慣包括是否抽菸、喝酒、嚼檳榔、運動、吃素，飲食調查包括牛奶或乳酪、海鮮類、蔬菜、水果、甜食、飲料、硝酸製品、肥肉、速食、咖啡等攝取頻率。個人疾病史包括糖尿病、高血壓、腦中風、心絞痛、心肌梗塞、腎臟病、痛風、脊椎側彎等疾病。父母親資料包括年齡、身高、體重、教育程度、職業、是否抽菸、是否喝酒、是否嚼檳榔、運動習慣、是否為素食者等。父母疾病史及家族疾病史調查的疾病包括糖尿病、高血壓、腦中風、冠心病、腎臟病、痛風、癌症等。

(2) 理學檢查

包括身高、體重、腰圍、臀圍、收縮壓、舒張壓等。

(3) 尿液檢查

尿液檢查包括總蛋白量(total protein, TP)、微白蛋白尿(microalbumine)、肌酸酐(creatinine, CRE)、白蛋白排出率(albumin excretion rates, AER)、鈉離子(Na^+)、鉀離子(K^+)、氯離子(Cl^-)、尿糖(urine glucose)、尿蛋白(urine protein)等檢查。

(4) 抽血檢查

血液檢查項目包括白血球(white blood cell, WBC)、紅血球(red blood cell, RBC)、血色素(hemoglobin, HB)、血小板(platelet)、嗜中性球(neutrophil)、嗜酸性

球(eosinophil, eosin)、嗜鹼性球(basophil, baso)、淋巴球(lymphocyte)、單核球(monocyte)、總膽固醇(total cholesterol, TCHO)、高密度膽固醇(high-density lipoproteins, HDL)、低密度膽固醇(low-density lipoproteins, LDL)、三酸甘油脂(triglyceride, TG)、鈉離子(Na^+)、鉀離子(K^+)、氯離子(Cl^-)、總蛋白量(total protein, TP)、白蛋白(albumin)、球蛋白(globulin)、尿酸(uric acid, UA)、尿素氮(blood urea nitrogen, BUN)、肌酸酐(creatinine)、glutamic-oxalacetic-transaminase (GOT)、glutamic-pyruvic-transaminase (GPT)、血糖(glucose)、胰島素(insulin)等。

(5) 頸動脈超音波檢查

頸動脈超音波所使用的儀器為 Sonosite Titan (Sonosite, Bothell, WA)，測量項目包括：總頸動脈(common carotid artery, CCA)的平均厚度與最大厚度、內頸動脈(internal carotid artery, ICA) 的平均厚度與最大厚度、頸動脈球體部動脈(bulb) 的平均厚度與最大厚度、頸動脈硬化塊分數(plaque score)、頸動脈血管內中皮層厚度(intima-mediate thickness, IMT)等。

(6) Colin 血管彈性量測

受測者進入檢查室後，以仰臥姿勢(supine)平躺在診察床上，五分鐘後進行量測。檢查室的溫度保持在 22-25°C。檢查前預先讓受測者排尿。在測量前請受測者做 2-3 次深呼吸。受測者穿著厚重衣物時請其脫掉，只留一件薄衣，穿著襪子時請其脫下，或退至露出後腳跟的程度。測量時間約 5 分鐘。第一次體驗下肢血壓測量時受測者容易緊張，以說明測量方法等來緩和受測者的心情。測量中告知受測者請勿移動身體並暫時不要說話。若數值與波形產生左右極大差異時，必須判斷是自於受檢者本身生理狀況或是測量者技術的問題。再決定是否需要重新測量。

第三節 資料分析

(一) 基線資料研究

1. 重疊病例對照研究(nested case-control study)

本研究先比較病例組與對照組之BMI、總膽固醇、BUN、肌酸酐、白蛋白等平均值之差異。連續性的測值再依照臨床的標準分成類別變項，如BMI≥27 kg/m^2、空腹血糖 ≥100 mg/dL、總膽固醇 ≥200 mg/dL等，以卡方檢定比較各變項在兩組間的差異。我們也利用Spearman correlation coefficient分析，檢視各連續性變項之間的相關性。最後挑選在單變項分析時有顯著的變項，以多變項羅吉斯迴歸(multivariate logistic regression)計算各變項與高血壓的危險比(odds ratio, OR)及95%可信限(confidence interval, CI)。因為BMI為兒童及青少年高血壓的重要因子，因此本研究也以BMI為主要因子做分層分析，探討BMI各分層與總膽固醇、BUN、肌酸酐、白蛋白等的加成效應及其對高血壓的影響。我們也將高血壓分為stage 1 (收縮壓 = 140-149 mmHg 或 舒張壓 = 90-99)和stage 2(收縮壓≥160 mmHg或舒張壓≥100 mmHg)高血壓，以探討少年BMI與嚴重高血壓的相關。

因不同尿液篩檢結果對兒童及青少年高血壓可能會有不同的影響，因此本研究將分別分析兒童及青少年高血壓在血尿、蛋白尿及尿糖中的盛行率及其相關因子。

2. 出生體重與兒童及青少年高血壓之研究

我們利用本研究的基線資料，串聯了出生登記資料庫，收集了這些尿液篩檢陽性學生的出生資料。經參考過去的文獻後，我們將出生體重分為< 2500 克、2500-2999 克、3000-3499 克、3500-3999 及≥ 4000 克。利用 ANOVA 比較五個出生體重類別的年齡、BMI、收縮壓、舒張壓、空腹血糖及總膽固醇平均值之差異。以卡方檢定比較各變項(性別、肥胖、高血壓、空腹血糖異常及高膽固醇)在出生體重間的差異。再以年齡及性別做分層分析，比較高血壓盛行率在不同的年齡層及性別之差異。再利用多變項羅吉斯迴歸做 4 個 Model 分別校正不同的相關因子，計算出生體重與高血壓的危險比及 95%可信限。最後再以肥胖做分層分析，分別計算肥胖者與非肥胖者的出生體重與高血壓之危險比。

3. IgA與兒童及青少年高血壓之研究

我們先將基線資料中的IgA分性別觀察IgA的分布。再分別以男性及女性觀察IgA的平均值隨著年齡的變化。經檢視IgA的分布及參考過去的文獻後，我們將IgA以十分位數分成十個類別。我們利用ANOVA比較十個IgA類別的年齡、BMI、收縮壓、舒張壓、空腹血糖及總膽固醇平均值之差異。以卡方檢定比較各變項(性別、肥胖、高血壓、空腹血糖異常及高膽固醇)在IgA類別間的差異。我們採用一般國際期刊論文的標準，來定義孩童肥胖(年齡及性別特定的BMI ≥ 95百分比)、高血壓(年齡及性別特定的收縮壓或舒張壓 ≥ 95百分比)、高膽固醇(總膽固醇 ≥ 200 mg/dL)及空腹血糖異常(空腹血糖 ≥ 100 mg/dL)。再利用多變項羅吉斯迴歸，以最低的十分位數為參考組，分別計算IgA與高血壓、空腹血糖異常、及高膽固醇的危險比及95%可信限。最後再以肥胖做分層分析，分別計算肥胖者與非肥胖者的IgA與空腹血糖異常之危險比。

(二) 少年高血壓追蹤研究

在尿液篩檢陽性的兒童及青少年高血壓之追蹤研究中，我們依照美國心臟學會的兒童血壓標準並稍做修改，將1992-2000年間中小學生尿液篩檢陽性並有高血壓的學生視為暴露組，無高血壓的學生做為非暴露組，進行前瞻性世代研究(prospective cohort study)。這項追蹤研究將分成兩部分觀察：

(1) 基線高血壓學生的世代變化

這部分的尿液篩檢陽性的兒童及青少年高血壓之追蹤，著重學生血壓的變化。我們將探討過去有高血壓的學生，目前血壓值的變化，以 paired t-test 方式分析基線血壓值、BMI、總膽固醇、白蛋白、肌酸酐及血中尿素氮，分別與目前的血壓值、BMI、總膽固醇、白蛋白、肌酸酐及血中尿素氮是否有顯著的改變。以 Spearman correlation coefficient 分析基線 BMI、血壓及生化值與目前的 BMI、血壓及生化值之相關性。我們也將分析這群高血壓學生目前罹患慢性病的疾病率，

包括高血壓、糖尿病、腎臟病及心臟病等。

另外，本研究也將用回溯性研究的方式，以目前有高血壓的人為病例組，無高血壓的人為對照組，進行病例對照研究，探討過去的 BMI、血壓及生化因子是否與目前的高血壓有相關。這部分將先用卡方檢定來分析類別變項，比較病例組與對照組兩組間各變項的分布差異，再用多變項羅吉斯迴歸計算各變項與高血壓的危險比及 95%信賴區間。

(2) 尿液篩檢陽性的兒童及青少年高血壓世代研究

我們將以 t 檢定(t-test)來比較暴露組與非暴露組之間的連續性變項(如血壓、BMI 及總膽固醇等)的平均數之差異。本研究也利用卡方檢定(Chi-square test)來分析問卷資料及少年高血壓檢查資料中的類別變項(categorical variable)，比較暴露組與非暴露組之間各變項的分布差異。連續性的測值依照臨床的標準來分類，如收縮壓 ≥ 140 mmHg 為高血壓、舒張壓 ≥ 90 mmHg 為高血壓、BMI ≥ 27 kg/m^2 為肥胖、腰圍過大(男性 ≥ 90 cm，女性 ≥ 80 cm)、腰臀比過大(男性 ≥ 0.9，女性 ≥ 0.8)等，這些類別變項也將用卡方檢定先做分析。我們將挑選與高血壓有關的重要因子及在單變項分析時有顯著($p < 0.05$)的因子，進行多變項羅吉斯回歸(multivariate regression)分析，計算與少年高血壓與後來成年的代謝症候群因子之危險比(odds ratio, OR)及 95%信賴區間(confidence interval, CI)。所有檢定方法皆以 p 值 < 0.05 為檢定水準。

另外，在追蹤過程中，本研究也曾請那些有高血壓的學生邀請他們的好朋友來做檢查，這一部分我們將會以過去中小學時代有高血壓的青少年為病例組，而病例組的好朋友做為對照組，進行病例對照研究。這部分的資料不列入本論文。

第四章　研究結果

(一) 基線資料分析

1. 重疊病例對照研究

這個部分研究包括了 62,308 名(62.7%)女學生和 37,042 名(37.3%)男學生。Table 2-1 顯示，男孩比女孩有較高的平均年齡(12.3±2.7 對 11.8±2.7 歲，$p < 0.0001$)、BMI(19.2±3.7 對 18.8±3.5 kg/m^2，$p < 0.0001$)、收縮壓(19.2±3.7 對 18.8±3.5 kg/m^2，$p < 0.0001$)、空腹血糖(89.1±28.7 對 87.5±27.0 mg/dL，$p < 0.0001$)、血中尿素氮(13.2±13.2 對 11.8±9.9 mg/dL，$p < 0.0001$)及肌酸酐(1.11±0.64 對 1.00±0.39 mg/dL，$p < 0.0001$)。高血壓(20.6%對 15.9%，$p < 0.0001$)及空腹血糖異常(15.8%對 13.0%，$p < 0.0001$)盛行率也是男孩較女孩高。但女孩比男孩有較高的總膽固醇平均值(166.3±34.1 對 160.5±40.5，$p < 0.0001$)及高膽固醇盛行率(12.8%對 10.3%，$p < 0.0001$)。

Table 2-2 依照 BMI 將學生分成正常、過重及肥胖三組比較高血壓(cases)與非高血壓組(controls)的血壓及生化等值。病例組的收縮壓、舒張壓及總膽固醇較對照組來得高且達統計顯著($p \leq 0.01$). 病例組與對照組的收縮壓及總膽固醇差異，胖小孩較瘦小孩明顯。相較於瘦小孩，肥胖小孩的第二級高血壓盛行率高出許多(22.5%對 6.0%，$p < 0.0001$)。

基線資料中的 99,350 位學生中，1,503 位具有糖尿但沒有血尿或蛋白尿。在我們的病例對照分析中，高血壓孩童比非高血壓孩童有較高的糖尿盛行率(3.1% vs. 1.0%，$p < 0.0001$，資料未列示). 相較於對照，學生有較高的 BMI、總膽固醇、白蛋白及較低的 GFR 其高血壓危險較高(Table 2-3). 病例組的肥胖盛行率約為對照組的 3 倍(17.9% vs. 6.1%, $p < 0.0001$)。多變項羅吉斯迴歸中分析也顯示 BMI 與高血壓危險有最強的相關(胖小孩的 OR = 3.45，95% CI = 3.20-3.72)，其次是總膽固醇，兩者與高血壓都有劑量效應的關係($p < 0.0001$). 高血壓危險與肥胖的關係在血尿陽性(OR 3.21, 95% CI = 2.87-3.58)、蛋白尿陽性(OR = 3.64, 95% CI =

3.26-4.06)及糖尿陽性的學生間(OR = 3.98, 95% CI = 2.66-5.94)，有些微的變化(Table 2-4)，糖尿陽性學生較高。

在 BMI 分層分析中，多變項羅吉斯迴歸顯示無論是男孩或女孩或各年齡層中，高血壓的危險比隨著 BMI 增加而增加(Table 2-5)。相較於年紀小的孩童，BMI 與高血壓危險在年紀較大孩童中較強。相較於 6-9 歲的體重正常小孩，16-18 歲肥胖孩童的高血壓危險比增加到 4.55 (95% CI = 3.51-5.90)。BMI 與高血壓危險之關係在總膽固醇及血中尿素氮有明顯的交互作用。在肥胖小孩中，高血壓危險似乎會隨著總膽固醇的增加、GFR 的降低而增加，但較高的白蛋白則可能略增加高血壓危險。相較於體重正常且總膽固醇 < 200 mg/dL 的孩童，胖小孩且總膽固醇 ≥ 250 mg/dL 有最高的高血壓危險(OR = 6.15, 95% CI = 4.12-9.18)。GFR < 60 ml/min/1.73 m^2 的胖小孩的高血壓危險比為 GFR ≥ 60 ml/min/1.73 m^2 且體重正常小孩的 5.14 倍(95% CI = 3.43-7.72)。

2. 出生體重與少年高血壓

Table 3-1 比較學童各出生體重階層的特徵，顯示高血壓盛行率與出生體重為 V-型關係。相較於出生體重 2500-2999 克的學生有最低的高血壓的盛行率(7.79%)，出生體重≥ 4000 克的學生有最高的高血壓盛行率(10.6%，p < 0.0001)，低出生體重小孩也有較高的盛行率(9.12%)。出生體重 2500-2999 克的孩童有最低的 BMI 平均值、平均血壓及肥胖盛行率，而這群孩童也是最年輕的，女孩比例最高的。

高血壓危險比與出生體重也呈現 V-型關係。以出生體重 2500-2999 克的孩童當參考組，低出生體重孩童的高血壓危險比為 1.2 (Figure 3-1)，此危險比從出生體重 3000-3499 克孩童的 1.1 增加到出生體重 ≥ 4000 克孩童的 1.4。經校正年齡及性別後，高血壓危險比在出生體重 ≥ 4000 克孩童降低為 1.3。再經校正 BMI 後，高血壓危險比與出生體重的 V-型關係再降低。

在各年齡層的男孩中，高血壓危險比與出生體重的 V-型關係明顯，尤其是有年紀較大的低出生體重孩童(Figure 3-2)。高血壓的盛行率在 16-18 歲的男孩中從出生體重 2500-2999 克的 12%增加到低出生體的 17%，此盛行率在出生體重 ≥ 4000 克的為 13.5%。另一方面，年紀較大(16-18 歲)的女孩有最低的高血壓盛行率，尤其是那些低出生體重或高出生體重的女孩。在女孩中，高血壓危險比與出生體重的 V-型關係只出現在 10-15 歲的女孩。

經校正年齡、性別及相關生化變項後，與出生體重正常(2500-2999 克)的學生相較，高血壓危險比在出生體重 3000-3499 克的學生為 1.09 (95% CI = 1.01-1.17)，出生體重≥4000 克的學生為 1.02 (95% CI = 0.90-1.14) (Table 3-2)。相較於體重過低的孩童，肥胖(OR = 9.84, 95% CI = 8.93-10.8)、體重過重 (OR = 4.20, 95% CI = 3.79-4.64)及體重正常孩童(OR = 1.89, 95% CI = 1.78-2.01)有較高的高血壓危險。相較於肥胖孩童，高血壓危險比與出生體重的 V-型關係在非肥胖孩童較明顯。出生體重每增加 1kg，不肥胖的小孩的高血壓勝算比增加 9%(95% CI = 3%-16%)，對肥胖小孩則無相關(Table 3-3)。

3. IgA 與兒童及青少年高血壓、血糖異常及高膽固醇

圖 4-1 為學童血清 IgA 的分布百分比。圖 4-2 為年齡及性別特定的 IgA 濃度平均值，無論是男孩或女孩，IgA 平均值隨著年齡增加而有上升的趨勢。在 92,514 位尿液篩檢陽性的學生中，IgA 濃度的中位數從最低層十分位數的 94 mg/dL 增加到最高層十分位數的 190 mg/dL (Table 4-1)。年齡($p < 0.0001$)、BMI($p < 0.0001$)、血壓($p < 0.0001$)、空腹血糖($p < 0.0001$)、及總膽固醇($p < 0.0001$)的平均值隨著 IgA 的增加而提高。女孩的比例在各 IgA 分層中有明顯的變動(最低十分位層：66.7%，最高十分位層：60.5%，$p < 0.0001$)。空腹血糖異常盛行率從 IgA 最低十分位層的 11%增加到最高十分位層 19%($p < 0.0001$)。高血壓盛行率也是由 7.5% 增加到 10.8% ($p < 0.0001$)。高膽固醇盛行率在 IgA 分層中也有顯著差異。多變項羅吉斯

迴歸分析顯示，相較於有最低 IgA 十分位數的學童，有最高 IgA 十分位數的學童有較高的高血壓(OR = 1.20，95% CI = 1.08-1.34)、高膽固醇(OR = 1.22, 95% CI = 1.11-1.34)及空腹血糖異常危險比(OR = 1.77，95% CI = 1.62-1.93) (Figure 4-3)。有最高十分位數的肥胖孩童其空腹血糖異常危險比增加到 2.93 (95% CI = 1.93-4.44) (Table 4-2)。

Table 4-3 顯示，血中 IgA 濃度每增加 100 mg/dL，高血壓危險比增加 5% (95% CI = 2%-8%)，高膽固醇及空腹血糖異常之危險比分別會增加 9%(95% CI = 6%-11%)及 23%(95% CI = 20%-26%)。不論是有血尿的學生(OR = 1.61，95% CI = 1.39-1.87)或是有尿蛋白的學生(OR = 1.44，95% CI = 1.28-1.63)，血中 IgA 濃度的升高都會增加空腹血糖異常之危險(Table 4-4)。

(二) 少年高血壓追蹤研究

經過將近十年的追蹤時間，本研究成功邀請了 988 位過去有尿液篩檢陽性學生接受追蹤檢查，其中 347 位為高血壓暴露組。相較於非暴露組，暴露組在孩童時期的 BMI(20.8±4.9 對 18.2±3.1 kg/m^2，$p < 0.0001$)、收縮壓(127.1±15.2 對 102.9±11.3 mmHg，$p < 0.0001$)、舒張壓(85.3.1±10.7 對 64.4±8.6 mmHg，$p < 0.0001$)、空腹血糖(87.8±29.3 對 83.7±12.1 mg/dL，$p = 0.015$)及總膽固醇(166.2±42.6 對 160.2±31.2 mg/dL，$p = 0.022$)平均值皆較高(Table 5-1)。孩童時期的肥胖(19.7%對 3.5%，$p < 0.0001$)、高血糖(12.7%對 8.7%，$p = 0.05$)及高膽固醇(13.8%對 9.2%，$p = 0.025$)盛行率也是暴露組較非暴露組高。

暴露組較非暴露組年輕(20.9±3.4 對 21.9±3.3 歲，$p < 0.0001$)，但暴露組比非暴露組有較高的 BMI(23.3±5.0 對 21.0±3.2 kg/m^2，$p < 0.0001$)、腰圍(75.4±13.9 對 69.2±9.1 cm，$p < 0.0001$)、收縮壓(113.0±16.7 對 105.6±12.2 mmHg，$p < 0.0001$)、舒張壓(71.9±13.0 對 65.8±9.7 mmHg，$p < 0.0001$)、三酸甘油脂(95.1±108.5 對 78.0±40.4 mg/dL，$p < 0.005$)及空腹血糖(89.6±29.5 對 83.8±9.8 mg/dL，$p = 0.0004$)平均值(Table 5-2)。HDL 平均值則是暴露組較非暴露組低(48.4±10.4 對 51.8±10.0 mg/dL，$p < 0.0001$)。非暴露組較暴露組多有喝酒的習慣(11.0%對 6.5%，$p = 0.022$)，但抽菸習慣在兩組間無顯著差異。相較於非暴露組，暴露組有較高的腹部肥胖(20.2%對 5.1%，$p < 0.0001$)、血壓過高(19.6%對 5.6%，$p < 0.0001$)、過低的 HDL(42.1%對 26.8%，$p < 0.0001$)、高三酸甘油脂(10.1%對 5.2%，$p = 0.003$)及血糖過高(6.9%對 2.0%，$p < 0.0001$)盛行率。

在非暴露中，孩童時期的收縮壓與目前的腰圍($r = 0.177$，$p < 0.0001$)、收縮壓($r = 0.204$，$p < 0.001$)、舒張壓($r = 0.141$，$p < 0.05$)有明顯相關(Table 5-4)。非暴露組孩童時期的舒張壓與目前的腰圍($r = 0.113$，$p < 0.05$)、收縮壓($r = 0.151$，$p < 0.0001$)、舒張壓($r = 0.128$，$p < 0.05$)也有明顯相關。在暴露組中，孩童時期的收縮壓與目前血壓較腰圍($r = 0.150$，$p < 0.05$)與收縮壓($r = 0.219$，$p < 0.0001$)有顯著

相關，孩童時期的舒張壓與目前的舒張壓也有相關(r = 0.221，p < 0.0001)。

表 5-5 的單變項分析顯示，相較於參考組的人，目前有腹部肥胖的人在尿酸篩檢時的基線收縮壓比無腹部肥胖的人高(123.8±19.2 對 109.9±16.4 mmHg，p < 0.0001)、目前血壓過高(123.7±17.8 對 109.9±16.6 mmHg，p < 0.0001)、高三酸甘油脂(119.1±18.3 對 110.8±17.0 mmHg，p < 0.0001)、血糖過高(121.8±23.2 對 111.0±16.9 mmHg，p = 0.008)及代謝症候群(127.8±20.2 對 110.7±16.8 mmHg，p < 0.0001)的人，孩童時期的基線收縮壓都較高。而舒張壓也有相同的情況。在對照組中，相較於沒有高血糖的人，有高血糖的人其兒童時期的平均舒張壓較低(59.3±10.7 對 64.6±8.6 mmHg，p = 0.03) (Table 5-6)。在暴露組中，相較於參考組的人，目前有腹部肥胖(132.4±16.5 對 125.7±14.6 mmHg，p = 0.001)、血壓過高(130.7±16.3 對 126.2±14.8 mmHg，p = 0.028)、高三酸甘油脂(132.5±11.5 對 126.4±15.5 mmHg，p = 0.006)、血糖過高(134.8±16.1 對 126.5±15.0 mmHg，p = 0.009)及代謝症候群(135.0±15.8 對 126.3±15.0 mmHg，p = 0.003)的人，孩童時期的收縮壓較高；以舒張壓來說，血糖過高的人較血糖正常者高(90.1±12.9 對 84.9±10.5 mmHg，p = 0.023)。

Table 5-7 顯示代謝異常因子越多的人，其收縮壓或舒張壓也越高。以收縮壓來看，血壓從沒有代謝異常因子的 108.9 (±16.0) mmHg 增加到有三個代謝異常因子的 127.7 (±20.2) mmHg (p < 0.0001)。舒張壓也有相似的情況，從 69.6 (±12.4) mmHg 增加到 80.9 (±19.2) mmHg (p < 0.0001)。Table 5-8 或 Table 5-9 比較基線暴露組和非暴露組的血壓和代謝症候因子之相關。暴露組的平均血壓比非暴露組的都較高，尤其是有三項代謝症候因子時，收縮壓高出 32.3 mmHg，舒張壓也達 28.6 mmHg。在非暴露組中，孩童時期的舒張壓在代謝異常因子上雖有顯著差異(p = 0.004)，但沒有隨著代謝異常因子的增加而增加。在暴露組中，孩童時期的收縮壓在代謝異常因子上雖有顯著差異(p = 0.001)，但也沒有隨著代謝異常因子的增加而增加。孩童時期有高血壓的人，孩童時期的收縮壓略有隨成年後代謝症候因子

增加而增加，而舒張壓增加的趨勢則更明顯(Table 5-9)。

Table 5-10 利用四個不同的羅吉斯迴歸模型來表示孩童高血壓與代謝異常的關係。經校正年齡及性別後(Model 1)，相較於沒有兒童高血壓的人，有兒童高血壓的人目前有較高的腹部肥胖(OR = 4.92，95% CI = 3.15-7.67)、血壓過高(OR = 4.26，95% CI = 2.72-6.68)、低 HDL(OR = 2.04，95% CI = 1.53-2.71)、高三酸甘油脂(OR = 2.07，95% CI = 1.25-3.42)、血糖過高(OR = 3.89，95% CI = 1.98-8.01)及代謝症候群(OR = 6.91，95% CI = 3.21-14.8)。在 Model 2 中(校正年齡、性別、教育程度、抽菸、喝酒及家族高血壓病史)，兒童高血壓仍與五個代謝異常因子及代謝症候群有關。在 Model 3 中(校正年齡、性別、教育程度、抽菸、喝酒、家族高血壓病史及 BMI)，除了高三酸甘油脂外，其餘的代謝異常都與兒童高血壓有顯著關係。Model 4 又多校正了胰島素、尿酸及 hsCRP，結果顯示兒童高血壓會增加後來成年的腹部肥胖(OR = 2.33，95% CI = 1.14-4.78)、血壓過高(OR = 4.19，95% CI = 2.42-7.28)、低 HDL(OR = 1.73，95% CI = 1.25-2.40)、血糖過高(OR = 4.70，95% CI = 1.62-13.6)及代謝症候群(OR = 4.20，95% CI = 1.23-14.3)之危險。

經校正其他心血管疾病的相關因子後，兒童時期的收縮壓每增加 5 mmHg，成年後的就會增加 10%的腹部肥胖(95% CI = 0%-21%)、20%的血壓過高(95% CI = 11%-30%)、23%的血糖過高(95% CI = 8%-41%)及 24%的代謝症候群(OR = 1.24，95% CI = 6%-44%)之危險比(Table 5-11)。以兒童時期的舒張壓來看(Table 5-12)，每增加 5 mmHg 的舒張壓，成年後的腹部肥胖危險比會增加 17%(95% CI = 2%-34%)，血壓過高增加 23%(95% CI = 12%-35%)，血糖過高會增加 18%(95% CI = 1%-37%)。

第五章　討論

(一) 基線資料

1. 重疊病例對照研究

本研究發現尿液篩檢陽性的兒童與青少年，高血壓盛行率高達 17.7%。在此病例對照研究中，不論是體重正常、過重或肥胖的學生，病例組的平均血壓都高於對照組，尤其是收縮壓，肥胖病例高於肥胖對照 21.8 mmHg。過去許多研究也曾報導過在一般兒童與青少年中的 BMI 與血壓的顯著關係[48, 54, 80-82]。西班牙的一項研究就曾經指出 6-16 歲的胖小孩無論是收縮壓或舒張壓都比體重正常小孩高。

經過回顧了 74 篇有關兒童肥胖與高血壓的文章，Sorof 與 Daniel 指出胖小孩有高血壓的危險比是體重正常小孩的三倍[83]。在休士頓 10-19 歲小孩中，相較於體重正常的小孩，胖小孩的高血壓危險比為 3.26[3]。本研究發現胖小孩較體重正常小孩的高血壓危險比為 3.45。這樣高的高血壓危險或許有些可歸因於尿液篩檢異常的問題。本研究也發現 BMI 與高血壓有劑量效應的關係，而這也意涵著 BMI 影響兒童高血壓甚鉅。根據文獻，少年時期的體重每降低一公斤，收縮壓即可減少 1.05 mmHg，舒張壓可減少 0.92 mmHg[84]。成年時期的肥胖會增加心血管疾病的危險，而少年時期的肥胖會增加成人肥胖的危險[82]。因此，兒童時期的肥胖問題不容忽視。

高膽固醇也是一個已知的高血壓危險因子[54, 85]。在荷蘭 5-18 歲的學童中，有高血壓的學生較無高血壓學生有較高的總膽固醇(4.3±0.8 vs. 3.9±0.6 mmol/L, $p<0.01$) [54]。在本研究中，膽固醇較高的孩童其高血壓危險也比較高。且對於有高膽固醇的肥胖小孩來說，BMI 與膽固醇之間的明顯的交互作用，更加重了高血壓的相關。這樣明顯的劑量效應交互作用現象在過去並未被報導過。這或許是因為尿液篩檢陽性學童比較有高血壓的傾向。

本研究也發現血中尿素氮、肌酸酐或 GFR 與高血壓有關，這樣的結果與過去的

研究一致。Klag 等人就曾經指出，在非裔美國人中血中尿素氮與血壓有關 [86]。血中肌酸酐是腎臟功能的一項重要指標，也與高血壓或心血管疾病有關 [87-89]。美國一項追蹤研究發現，當血中肌酸酐濃度增加兩倍時，血壓會上升 20 mmHg [90]。而美國的第三次國民營養健康調查中也發現，高血壓患者其高肌酸酐危險為無高血壓的 9 倍[88]。

此外，美國的營養與健康調查也發現血中白蛋白過高與血壓、中風及冠心病有明顯相關[91]。挪威的一項研究也發現當血中白蛋白濃度增加到 4-5g/d 時，男性的收縮壓會上升 5-11 mmHg，女性的收縮壓會上升 6-17 mmHg[92]。但過去觀察血中白蛋白與血壓的研究都只限於成人，少有研究針對兒童與青少年來探討。本研究觀察到兒童血中白蛋白也與高血壓有關，雖然這樣的相關性可能不如成年人，但兒童血中白蛋白與高血壓之關係在胖小孩中更強烈些。

本研究的對象都是尿液篩檢異常(血尿、蛋白尿或糖尿)的學生，因此對照組為無高血壓但有尿液篩檢異常的學生，他們並不是真正健康的族群，因此缺乏健康對照組是本研究主要的研究限制之一。本研究所估計的高血壓危險可以代表有尿液篩檢問題孩童，推論到一般族群則需慎重，本研究可能稍低估了各因子間的相關。因此對於兒童高血壓與較高的血中白蛋白、肌酸酐或尿素氮有關，這樣的發現我們並不驚訝。若可以有健康對照組來做比較的話，高血壓的危險比將會更高[89-92]。本研究只做了一個時間點的(One-occasional)血壓量測，因此我們並不確定這些有高血壓的孩童是不是真的持續有高血壓，或只是當時量測時血壓過高而已，而這也是本研究的另一個研究限制。然而，若我們可以實行三個時間點(Three-occasional)的血壓篩選，相信我們應該可以觀察到更強烈的肥胖與高血壓之關係[3]。

在這群尿液篩檢陽性的兒童及青少年中，本研究發現 BMI 與高血壓存在著很強的劑量效應關係。在本研究中，肥胖是與高血壓有關的最重要因子，其次是高血脂、血中尿素氮過高、肌酸酐及白蛋白。兒童高血壓的重要性不容忽視，且

我們建議應針對肥胖小孩做例行性血壓檢查。需要後續研究進一步探討兒童與青少年高血壓對後來成年後的健康影響。

2. 出生體重與少年高血壓

人體的健康與出生狀況複雜的交互作用有關。本研究發現較高的出生體重和低出生體重均會增加孩童高血壓的危險，這樣的關係在非肥胖孩童中更為顯著。過去的文獻探討出生體重與兒童高血壓之關係時，很少將血液生化測量列入考慮。但對於出生體重與兒童高血壓之關係，血液生化測量非常重要，因為血脂肪及其他因子都是重要的心血管相關因子。

過去文獻報導低出生體重可能是成人心血管疾病的危險因子[93, 94]。但或許因為回憶性誤差[62]、沒有校正生化測量項目[60, 62, 95-98], 樣本數過小(438 位女性) [98]、低出生體重定義不適當(≤ 3450 克) [60] 或只針對懷孕女性做的研究[97]，過去的研究因此觀察到低出生體重與高血壓有關。本研究顯示低出生體重與高血壓的危險比為 1.11，但不顯著，美國孩童[99]、瑞典男性[100]的研究結果也有類似的情形。目前低出生體重與高血壓研究結果不一致，需要設計良好的後續研究來做進一步的探討。

過去的研究也發現高出生體重與高血壓危險有關[61]。本研究結果顯示相較於出生體重正常(2500-2999 克)學童，高出生體重(≥4000 克)學童增加了 19%的高血壓危險。因此高出生體重與高血壓之關係與過去文獻的研究結果是一致。

若嬰兒的出生體重較重，日後在兒童或青少年時期體重也可能較重，因此肥胖在出生體重與兒童高血壓之間可能扮演干擾因子的角色。在本研究中，出生體重與高血壓的相關強度不如 BMI 的強烈。

少年時期血壓的變動或許可源自於胎兒時期的發展。但出生體重與高血壓的關係並不只是受到遺傳的影響而已，後天的環境更是重要[60]。血壓的變異深受環境與生活型態所影響，不單單只是出生體重[101]。對於少年時期的血壓而言，兒童時期的因子較胎兒時期因子更為近期且影響更大[102]。SHARP (Scottish Heart

and Arterial Disease Risk Prevention)研究認為性別和BMI比出生體重對血壓的影響更大、更重要[103]。我們的資料也顯示兒童及青少年高血壓與出生體重的關係不及BMI的強。因此對兒童肥胖的介入應有助於高血壓的預防。另外，兒童時期血壓的變異也受兒童家庭之社經地位所影響[42]。若能了解兒童的家庭社經地位及環境將有助於探討出生體重與高血壓之關係[104]。

雖然已經有很多研究發現出生體重與血壓之關係，大部分的這類研究以成人為對象，尤其是四、五十歲之後高血壓盛行之年齡。由於血壓和年齡有正相關，出生體重和血壓的相關，年青人及小孩可能有異於成人。有些研究認為出生體重與兒童血壓沒有顯著關係[100, 104-106]。Hardy 等人認為從兒童時期到中年時期不管是在那個年齡層，出生體重與收縮壓都沒有顯著的關係，但體重的控制在每個年齡層都是預防血壓升高的關鍵[104]。本研究以青少年為對象，出生體重的血壓相關，雖然不如 BMI，但我們觀察到男孩的相關明顯，女孩則較弱，但 16-18 歲女生的反 V 型相關則需繼續探討。

雖然本研究有觀察到重要的結果，但本研究仍有些資料上的限制。第一， 本研究一開始就排除了12588位沒有出生資料的學生及1500位學生有出生資料但出生體重資料遺失。但就我們所知，被排除掉的學生與本研究的對象在年齡及性別上並無顯著差異。第二，本研究缺乏這些學生的心血管疾病史及家庭社經地位之資料。出生體重對兒童血壓的影響並非父母親的因子所干擾，但許多研究都發現父母親的因子對子女的健康會有影響[33, 81]。第三，本研究對象皆為尿液篩檢陽性學童，並不是一般健康的兒童及青少年，因此將本研究結果推論到一般健康族群是有些保留，但所顯現的結果和一般研究結果相當一致。

總之，本研究結果顯示高出生體重對增加體重正常的兒童及青少年之高血壓危險，但出生體重與孩童高血壓之關係不如 BMI 來得強烈。對於預防青少年乃至後續成年高血壓，青少年的肥胖預防極為重要。

3. IgA 與兒童及青少年高血壓、血糖異常及高膽固醇

從這群尿液篩檢陽性兒童及青少年中，本研究發現 IgA 濃度過高與空腹血糖異常之危險存在劑量效應之關係。過去的台灣尿液篩檢計畫顯示青少年糖尿病對後來生活健康影響極大[51]。這樣的影響或許部分可歸因於 IgA 的發炎反應。本研究也發現，高 IgA 與高血壓及高膽固醇也有關。

過去也有研究發現高膽固醇或糖尿病人血中的IgA濃度會上升，但這些研究只限於成人族群[68, 69, 107]。本研究發現兒童與青少年的高濃度IgA與空腹血糖異常有關，而就我們所知，這是過去研究不曾報告過的。發炎反應與代謝問題關係強烈。如hs-CRP、白血球及IgA濃度都可視為發炎反應的指標，而發炎反應指標與代謝異常有關，尤其是空腹血糖異常[108]。目前兒童及青少年的空腹血糖異常及第二型糖尿病的盛行率漸增已受到關注，而這兩者都會增加心血管疾病的危險，在公共衛生方面有很大的意涵[51, 58, 109-111].

過去也有研究發現高濃度的發炎敏感性的血漿蛋白與高膽固醇血症有關[112, 113]。一項針對成人族群的研究指出，IgA 濃度與總膽固醇有明顯相關[67]。另一項研究報告相較於血脂正常之成人，血脂異常(高三酸甘油脂或低 HDL)的成人有較高的 IgA[69]。但目前仍無任何研究報導少年的 IgA 與總膽固醇之關係，因此本研究可說是探討兒童及青少年 IgA 與總膽固醇的先驅研究。人體中的總膽固醇會被低度發炎反應而影響[114]，但這其中的機制仍不明確。Engström 等人建議發炎反應與高膽固醇血症的關係強度並不強，但高膽固醇血症會增強發炎反應與心血管疾病之關係[112, 113, 115]。

高濃度的發炎敏感血漿蛋白與血壓過高有關[115]。無論是流行病學研究或是生物性研究都認為發炎反應與高血壓有關[116]。發炎反應也可預測成人的高血壓前期[117, 118]。甚至低度的發炎反應也可在白袍高血壓的成人中觀察到[119]. 本研究發現，高濃度的 IgA 與兒童及青少年高血壓有關。雖然如此，許多研究認為發炎反應在高血壓的病理扮演重要角色，但仍缺乏明確的證據[120]。

本研究觀察到 IgA 與代謝異常之關係並不令人驚訝，但 IgA 增加代謝異常危

險的機制仍不明確。而代謝異常更會加深 IgA 腎臟病變的問題。因為本研究對象為尿液篩檢異常(蛋白尿、血尿及糖尿)學生，因此或許有一小部分的學生可能有 IgA 腎臟病變。但我們卻不知這群學生的 IgA 腎臟病變盛行率為何，而這也是本研究的限制之一。

抽菸、喝酒及飲食都是與發炎反應有關的因子[69, 121-124]。但我們無法獲得關於這群學生的抽菸、喝酒或其他生活型態資料，這也是研究限制之一。. 然而，抽菸與喝酒所引起的發炎反應對這群學生的影響有限，因為台灣學生抽菸與喝酒的盛行率相對很低。最近的研究也報導空氣污染物會引起發炎反應，而缺乏空氣污染資訊也是本研究的限制[108, 125]。

本研究發現兒童與青少年血中 IgA 濃度過高，與空腹血糖異常、高膽固醇及高血壓有關。IgA 與這些代謝異常因子的作用機制不明。因此後續研究需進一步確認 IgA 與代謝異常的相關作用機制。

(二) 少年高血壓追蹤研究

本計畫的首要目的是探討在青少年期間經尿液篩檢陽性又有高血壓的人，在十年後對健康之影響。結果顯示，347 位原先為高血壓組的小孩，只有 4.4%仍可判定為高血壓，但比對照組原先無高血壓而有 0.3%出現高血壓情況。這個結果說明絕大部分的少年高血壓是暫時性的。不過，會持續有高血壓的危險仍然存在，仍有 15 倍之多，平均收縮壓高出 7.4 mmHg，平均舒張壓高出 6.1 mmHg，男性又勝於女性，說明男性有早發高血壓的問題。暴露組持續有較高的 BMI 及腰圍，顯示高血壓的相關因子一直是存在的。

相較於沒有被追蹤的學生，追蹤研究中的 988 位個案的男性比例較低(38.9%對 43.5%，$p < 0.0001$)，年齡較高但不顯著。從兒童到老年，年齡與性別一直是影響血壓的重要因素[17, 126]，通常年齡越大其血壓值越高。本研究目前所收集的病例組約較對照組年輕一歲，且年齡≥20 歲的比例較低(66.9%對 74.6%，$p = 0.01$)，

而暴露組的收縮壓與舒張壓平均值都較非暴露組高，說明病例組有較高的高血壓盛行率，並非年齡使然。性別比例在兩組間則無顯著差異。

本研究的主要目的在探討少年高血壓對後來的健康影響，特別是心血管疾病及代謝異常的問題。肥胖是高血壓的危險因子之一，而對於兒童及青少年的高血壓來說，兒童肥胖更是重要因子，且少年肥胖與成年後的肥胖也有相關[38]，肥胖甚至會影響從青少年至老年的動脈硬化[38]。本研究暴露組目前的 BMI 及腰圍平均值都比非暴露組來的高，且肥胖(BMI ≥ 27 kg/m^2)及中央型肥胖(central obesity)的盛行率也是暴露組較非暴露組高。經過校正後，相較於非暴露組，暴露組的中央型肥胖(OR = 2.33)的危險比較高。對心血管疾病的影響，腹部的肥胖比身體質量肥胖更為重要[126-128]。暴露組有較高的腹部肥胖危險，這或許表示暴露組有較高的潛在性心血管疾病危險。

我們的研究發現，暴露組目前的收縮壓及舒張壓平均值都比非暴露組高，且高血壓的盛行率也是暴露組較非暴露組高。經過校正後，相較於非暴露組，暴露組的血壓過高之危險比為 4.19 (95% CI = 2.42-7.28)。這樣的結果與過去的研究相似。Sun 等人[77]發現，兒童時期的收縮壓過高，會增加成年後的高血壓危險。可見少年高血壓的問題不容忽視。

血脂肪方面，相較於非暴露組，暴露組有較高的三酸甘油脂(triglyceride, TG)及較低的高密度脂蛋白膽固醇之平均值。HDL 過低及高三酸甘油脂的盛行率也是暴露組較非暴露組高。目前已有許多研究探討三酸甘油脂與少年高血壓的關係[16, 48, 53, 129]，相較於無高血壓少年，有高血壓的少年有較高的三酸甘油脂平均值、較低的 HDL 平均值，有高血壓的少年之高三酸甘油脂及 HDL 過低的比例也較高。本研究的結果顯示，相較於非暴露組，暴露組有較高的 HDL 過低(OR = 1.73)危險比。暴露組的高三酸甘油脂危險雖較非暴露組高，但經過校正後就不顯著。目前很少有研究估算血脂異常與少年高血壓的危險比。

兒童肥胖會增加高血壓及高血糖的危險[3, 51]。而兒童高血壓與高血糖有很

強的關係[51]。本研究也顯示暴露組的飯前血糖平均值比非暴露組來的高，且暴露組的血糖異常(≥100 mg/dL)盛行率比非暴露組高。經過校正後，暴露組較非暴露組有較高的血糖異常危險比(OR = 4.70)。

最近十年國際間對代謝症候群的問題做了很多研究，其中也有研究探討兒童代謝症候群的問題[59, 75, 77, 130]。在本研究中，暴露組的代謝症候群盛行率為8.6%，高於非暴露組的 1.4% ($p < 0.0001$)。到目前為止，過去有關兒童與青少年時期有高血壓會增加日後代謝症候群危險的研究仍不多[77]。根據 Sun 等人對美國學童的研究，兒童時期的收縮壓過高，會增加成年後(≥ 30 歲)的高血壓(OR = 4.5，95% CI = 1.1-17.7)及代謝症候群之危險比(OR = 3.1，95% CI = 1.0-9.7) [77]。但這項研究的統計 model 並沒有考慮家族高血壓、尿酸、胰島素及 C 反應蛋白等相關因子的影響，而這些因子都是過去研究報導與兒童及青少年代謝症候群的相關因子[59, 75, 131, 132]。根據 1999-2002 年的美國國家營養健康調查對 12 至 17 歲的少年的研究，相較於血中尿酸濃度 < 4.9 mg/dL 的少年，血中尿酸濃度 > 5.7 mg/dL 的少年其代謝症候群的危險比高達 14.8 (95% CI = 7.8-28.1)。另外，抽菸(OR = 2.17, 95% CI = 1.49-3.18) [131]與喝酒(RR = 1.63, 95% CI = 1.02-2.62) [132]也是成人代謝症候群的危險因子，這兩者的盛行率在兒童與青少年中雖不高，但在探討少年代謝症候群時仍須考慮其影響。近十年來的少年高血壓有增加的趨勢[142-148]。以兒童與青少年來說，BMI 是目前被認為與高血壓關係最強的因子[133-141]，而 BMI 也是目前被認為與代謝症候群關係最強的因子[59, 75, 77, 130]。代謝症候群被認為是第二型糖尿病及心血管疾病的前驅[149]。血壓過高與後續發生的高血糖症，可能是多因子相關[150]，雖然個人與父母親間的相關因子仍然重要，環境因子也可能和兒童與青少年的心血管疾病及代謝健康問題有關，值得關注 [151]。Irace 等人發現，相較於有代謝症候群但沒有高血壓的人，有代謝症候群且有高血壓的人有較高的頸動脈硬化危險[152]。Ley 等人在經過十年的追蹤後，發現青年時期的高血壓會增加中年的第二型糖尿病之危險[153]。但 Ley

等人的這項研究只校正了年齡與性別。其他因子如身體質量指數及血脂肪都曾被報導與高血壓及糖尿病有明顯相關，應該在預測模式中被考慮。

本研究利用多變項羅吉斯迴歸，校正年齡、性別、教育程度、抽菸、喝酒、家族高血壓史、目前的 BMI、胰島素、尿酸及 C 反應蛋白後發現，相較於無少年高血壓的人，有少年高血壓的人在成年後產生代謝症候群危險比為 4.21 (95% CI = 1.23-14.3)。本研究的少年高血壓與成年高血壓的相關狀況和 Sun 等人[77]的研究相近，與代謝症候群的相關則較強些，顯示本研究結果和一般人口(general population)的差異不大。但 Sun 等人[77]的研究並未調整教育程度、抽菸、喝酒、家族高血壓史、胰島素、尿酸及 C 反應蛋白等因子。

第六章　結論與建議

高血壓盛行率在這群尿液篩檢陽性的兒童及青少年中相當高。肥胖是與高血壓有關的最重要因子，且 BMI 與高血壓存在著很強的劑量效應關係。高血脂、血中尿素氮過高、肌酸酐及白蛋白也與少年高血壓有相關。高出生體重及出生體重過低會增加體重正常的兒童及青少年之高血壓危險，但出生體重與孩童高血壓之關係不如 BMI 來得強烈。兒童與青少年血中 IgA 濃度過高，與空腹血糖異常、高膽固醇及高血壓均有關，但與血糖異常的相關較高。IgA 與這些代謝異常因子的作用機制仍不明。兒童與青少年時期有高血壓的人，在剛成年初即增加代謝症候群及代謝異常之危險，如：中央型肥胖、血壓過高、血脂異常、及空腹血糖異常等。

兒童高血壓的重要性不容忽視，肥胖小孩是高危險群，需做例行性血壓檢查。對於預防孩童高血壓來說，兒童肥胖極為重要。另外，血中 IgA 與糖尿病及代謝異常的相關作用機制需有進一步的研究來確認。本研究建議兒童與青少年高血壓對後來成年後的健康影響需持續監測。

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Table 1-2. Prevalence of hypertension among children and adolescents among countries

Country	Year	Population	Age	Prevalence, %			Reference
				Total	Boys	Girls	
Belgium		1,526	12-17	11.4			[142]
Belgium	1999	200	16-19	3.2	5.0	2.0	[31]
Brazil, Amazon		649	10-18	3.8			[143]
Brazil		479	6-12	22.0			[15]
Brazil, Alagoas	2000-2002	1,253	7-17	9.4			[144]
Canada, Quebec	1999	3,589	9-16	12.2	14.1	10.3	[145]
Denmark	1996-1997	16,680	15-20	18.5	20.0	17.6	[141]
Hungry	1997-2000	6,345	15-18	4.2	7.5	1.1	[146]
Hungry, Debrecen		10,359	14-18	2.3			[147]
India		5,000	5-17	0.5			[14]
India	2004	3,326	11-17	5.8			[24]
Iran	2003-2004	21,111	6-18	7.7			[34]
Israel		6,282	13-17	0.8			[148]
Israel	1996-2002	560,588	16-19	3.9			[45]
Italy, Milan	2003	2,416	6-11	4.2			[122]
Pakistan	1990-1994	5,641	5-14	12.2	15.8	8.7	[133]
Portugal		889	5-18	5.2			[134]
South Africa, Ellisras	2000	1,884	6-13	4.6	3.11	6.21	[135]
Switzerland	2005-2006	5,207	10-15	2.2			[41]
Taiwan, Taipei		1,366	12-16	17.1	17.5	16.6	[10]
Turkey		4,026	7-18	4.3	3.8	4.8	[136]
Turkey, Gemlik	1994	3,641	13-18	4.4			[137]
USA, Houston	2002	5,102	10-19	4.5			[3]
USA, New York	1970	3,573	14-19	7.8			[138]
USA, Minnesota		19,452	10-15	3.5			[139]
USA, Houston		2,460	12-16	16.8			[44]
USA, 3 cities	2003	1,717	12-14	13.8			[19]
USA, Delaware	2002	18,618	2-19	7.2	7.5	6.7	[140]
USA, Delaware	1996-2004	497	2-18	6.8			[48]
USA, Oklahoma	2001-2002	769	4-18	2.8			[37]
USA, Louisiana	1973-1994	9,167	5-17	5.9			[35]

Table 1-3. Birth weight and risk of hypertension

Author, year	Sample size	age	Country/ Population	Birth weight classification	Reference group	Risk factors
Kelishadi [34]	21111	6-18	Iran	<2500, 2500-4000, >4000	2500-4000	<2500 (OR=2.5, CI=1.7-3.5)
Gunnarsdottir, 2002 [60]	4601	33-65	Iceland	≤3450, 3460-3750, 3760-4000, >4000	3760-4000	≤3450 (OR=1.4, CI=1.1-1.8) in women
Tian, 2006 [61]	973	15-74	China	<2500, 2500-2999, 3000-3499, ≥3500	2500-2999	<2500 (OR=2.1, CI=1.1-3.8) ≥3500 (OR=2.1, CI=1.4-3.2)
Tamakoshi [62]	3107	35-66	Japan	<2500, 2500-2999, 3000-3499, ≥3500	2500-2999	OR=1.26 for <2500, OR=1 for 2500-2999, OR=0.89 for 3000-3499, OR=0.70 for ≥3500, p for trend=0.009
Bergvall, 2007 [63]	16265	42-74	Sweden	<1999, 2000-2499, 2500-2999, 3000-2499, ≥3500	2500-2999	2000-2499 (OR=1.5, CI=1.1-1.9) per 500g decrease (OR=1.4, CI=1.3-1.6)
Johansson, 2005 [64]	329495	18-19	Sweden/ men	BW<2SD, BW±2SD, BW>2SD	BW±2SD	BW<2SD (OR=1.3, CI=1.1-1.6) in GA = 33-36weeks, OR=1.1 (CI=1.0-1.2) in GA = 37-41weeks, OR=1.3, (CI=1.1-1.6) in GA = 33-36weeks
Hemachandra, 2007 [65]	55908	7	USA	-	-	per 1kg decrease, OR=2.2 (CI=1.9-2.5) of High SBP, OR=1.8 (CI=1.6-2.1) of high DBP
Longo-Mbenza, 1999 [99]	2648	--	Congo	<2500, ≥2500	≥2500	<2500, OR=2 (CI=0.9-8.2) in high SBP, OR=2.3 (CI=0.6-11) in high DBP

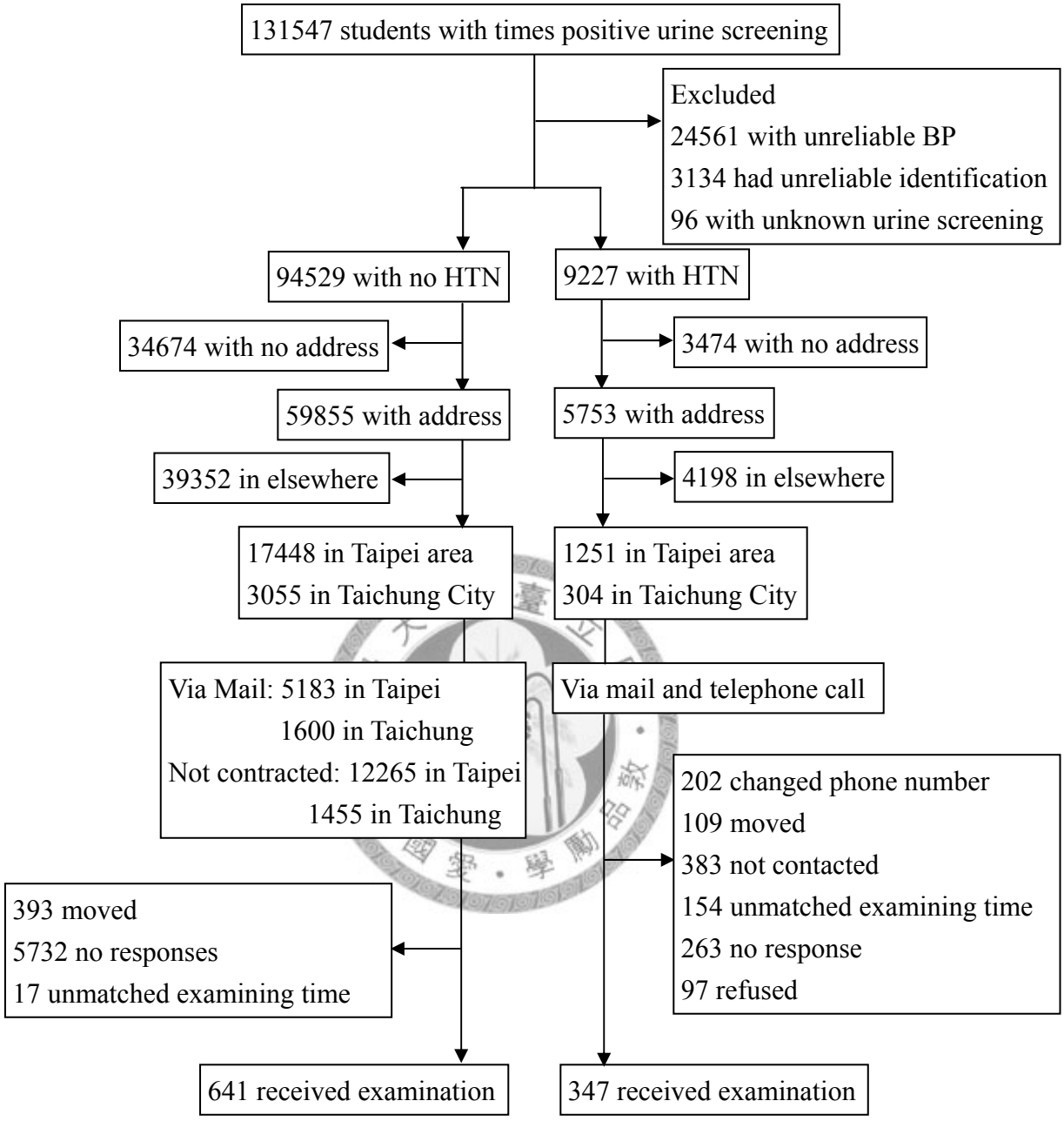


Figure 1-1. Procedure for selecting hypertensive cases and controls in the follow-up study

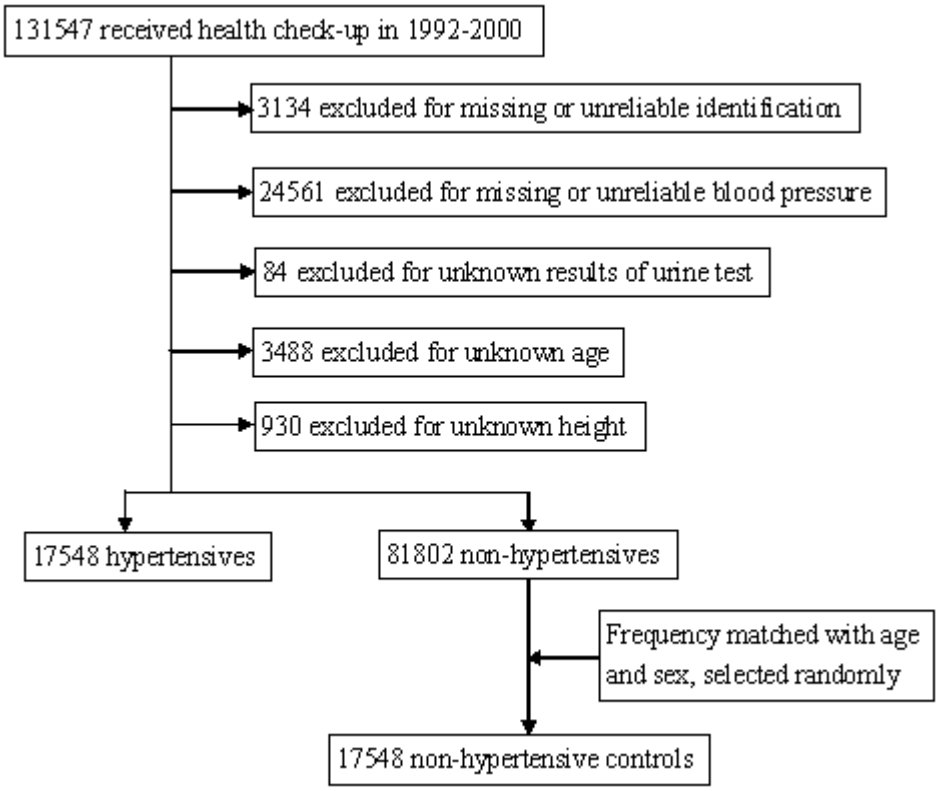


Figure 2-1. Procedures to select hypertensive cases and controls

Table 2-1. Comparison between girls and boys in baseline characteristics of all school children with positive urine screening

	Girls	Boys	Total	
Characteristics	Mean ± SD	Mean ± SD	Mean ± SD	p-value
Number	62308	37042	99350	
Age, years	11.8 ± 2.7	12.3 ± 2.7	12.0 ± 2.7	<0.0001
Body mass index, kg/m^2	18.8 ± 3.5	19.2 ± 3.7	19.0 ± 3.6	<0.0001
Systolic BP, mmHg	106.1 ± 13.5	111.1 ± 14.8	108.0 ± 14.2	<0.0001
Diastolic BP, mmHg	67.4 ± 10.4	69.0 ± 10.9	68.0 ± 10.6	<0.0001
Fasting glucose, mg/dL	87.5 ± 27.0	89.1 ± 28.7	88.1 ± 27.6	<0.0001
Total cholesterol, mg/dL	166.3 ± 34.1	160.5 ± 40.5	164.1 ± 36.7	<0.0001
Albumin, mg/dL	4.37 ± 4.30	4.36 ± 3.92	4.37 ± 4.16	0.66
Blood urea nitrogen, mg/dL	11.8 ± 9.9	13.2 ± 13.2	12.4 ± 11.3	<0.0001
Creatinine, mg/dL	1.00 ± 0.39	1.11 ± 0.64	1.05 ± 0.50	<0.0001
Hypertension, %	15.9	20.6	17.7	<0.0001
Impaired fasting glucose, %	13.0	15.8	14.0	<0.0001
Hypercholesterol, %	12.8	10.3	11.9	<0.0001

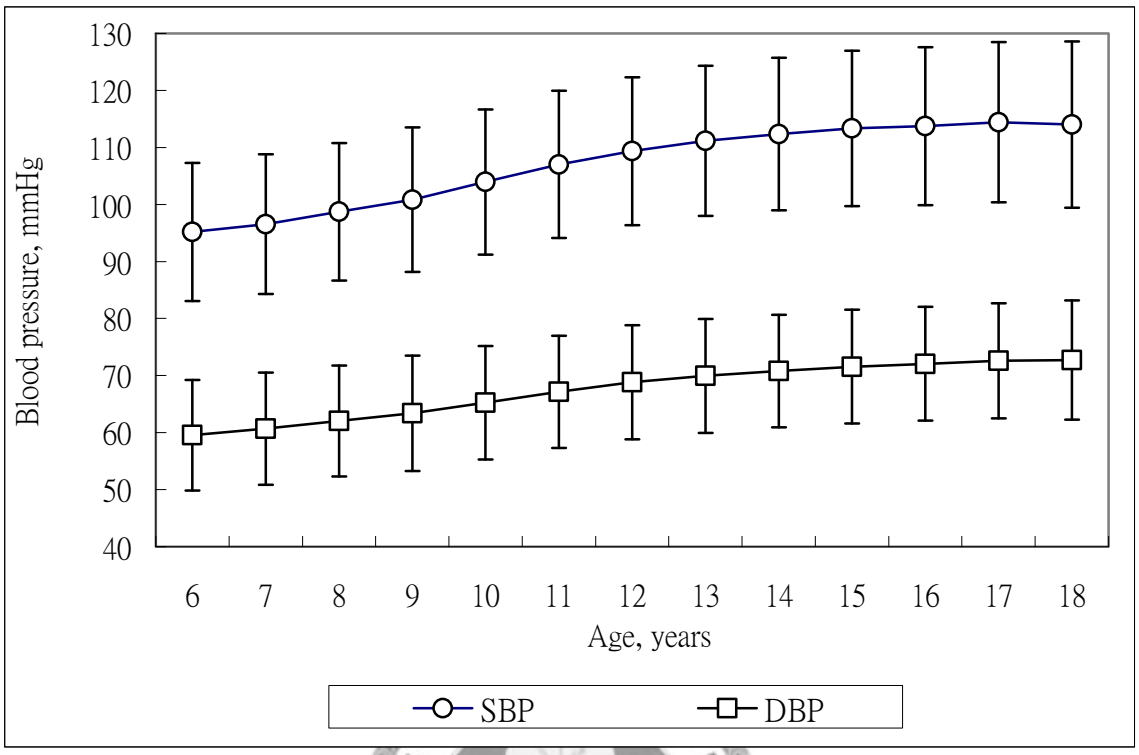


Figure 2-2. The average of blood pressures by age

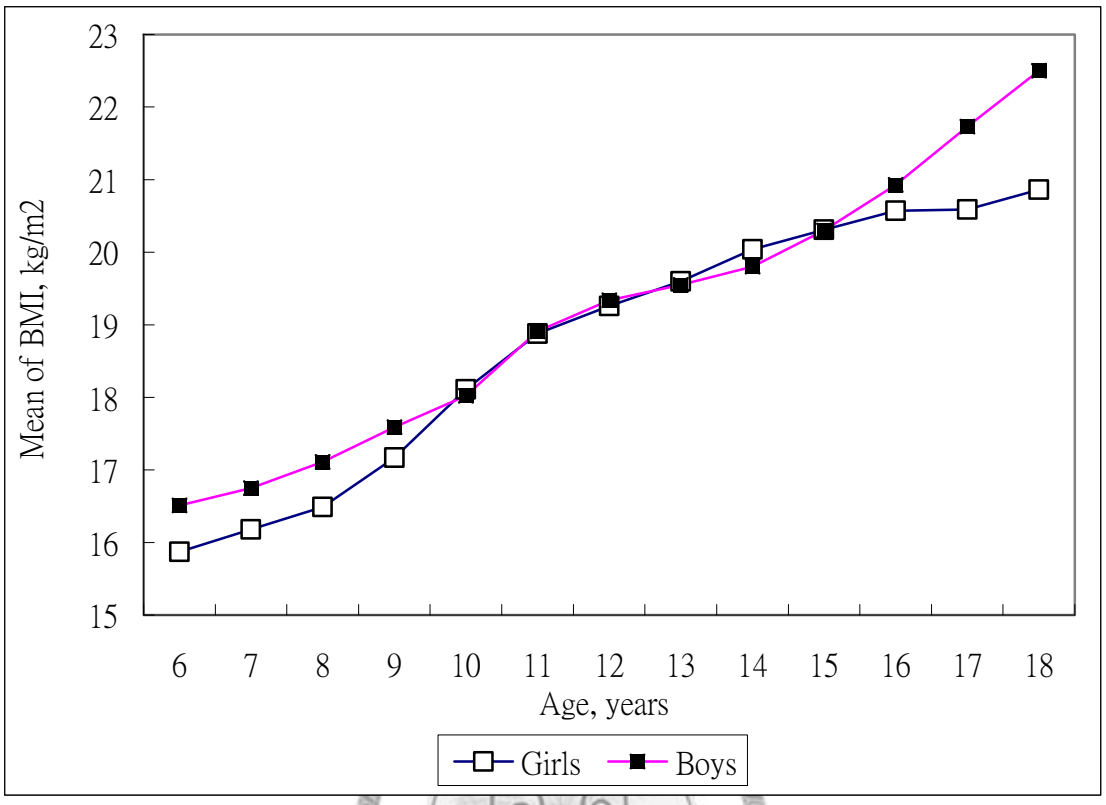


Figure 2-3 Body mass indexes by sex and age

Table 2-2. Comparisons between cases and controls in means of blood pressure, cholesterol, serum albumin, blood urea nitrogen and serum creatinine by body mass index

	Status of body mass index			
	Normal weight BMI < 85 percentile N=26722	Overweight 85 ≤ BMI < 95 percentile N=4050	Obesity BMI ≥ 95 percentile N=4181	*p* for trend
SBP, mmHg	Mean ± SD	Mean ± SD	Mean ± SD	
Cases	123.4 ± 11.5	125.6 ± 11.4	130.2 ± 13.5	< 0.0001
Controls	104.3 ± 11.3	106.6 ± 11.3	108.4 ± 11.0	< 0.0001
Difference	19.16	18.92	21.80	< 0.0001†
*p**	<0.0001	<0.0001	<0.0001	
DBP, mmHg				
Cases	79.3 ± 9.3	79.1 ± 9.0	81.7 ± 10.4	< 0.0001
Controls	65.2 ± 8.7	66.3 ± 8.6	67.5 ± 8.4	< 0.0001
Difference	14.08	12.86	14.15	0.5349†
*p**	<0.0001	<0.0001	<0.0001	
TCOL, mg/dL				
Cases	164.7 ± 39.1	168.4 ± 46.2	178.1 ± 46.0	< 0.0001
Controls	160.5 ± 34.6	163.0 ± 33.8	168.9 ± 37.8	< 0.0001
Difference	4.21	5.35	9.13	0.0001†
*p**	<0.0001	0.0052	<0.0001	
Albumin, mg/dL				
Cases	4.40 ± 4.07	4.37 ± 1.21	4.35 ± 0.42	0.4705
Controls	4.33 ± 0.67	4.33 ± 0.39	4.74 ± 13.2	0.0009
Difference	0.07	0.04	-0.39	0.0019†
*p**	<0.0001	0.0877	0.0436	
BUN, mg/dL				
Cases	12.36 ± 5.67	12.29 ± 5.68	12.57 ± 3.59	0.1093
Controls	12.38 ± 11.6	12.28 ± 4.86	12.62 ± 4.15	0.4705
Difference	-0.02	0.01	-0.06	0.9093†
*p**	0.2377	0.3088	0.5410	
Creatinine, mg/dL				
Cases	1.06 ± 0.34	1.11 ± 2.25	1.08 ± 0.24	0.1168
Controls	1.05 ± 0.24	1.04 ± 0.23	1.06 ± 0.35	0.1930
Difference	0.01	0.06	0.02	0.4192†
*p**	0.0553	0.3351	0.0016	
GFR				
Cases	90.2 ± 23.5	90.7 ± 20.0	90.3 ± 20.4	0.5600
Controls	90.6 ± 20.4	90.0 ± 21.0	90.0 ± 21.1	0.7709
Difference	-0.39	0.68	0.32	0.9204†
*p**	0.0578	0.2123	0.6118	
HTN stage 1, %	38.7	49.6	52.2	< 0.0001
HTN stage 2, %	6.0	9.5	22.5	< 0.0001

SBP, systolic blood pressure; *DBP*, diastolic blood pressure; *TCOL*, total cholesterol;

BUN, blood urea nitrogen; *GFR*, glomerular filtration rate; *HTN*, hypertension; *Wilcoxon rank sum test between cases and controls; †Test for interaction between difference and BMI status

Table 2-3. Comparisons between cases and controls by sex, age, body mass index and selected physiological examinations with univariate and multivariate logistic regression analyses

	Controls	Cases	Univariate	Multivariate
	N=17548	N=17548	OR (95% CI)	OR (95% CI)
Sex	%	%		
Girls	56.5	56.5	Reference	Reference
Boys	43.5	43.5	1.00 -	0.97 (0.93-1.02)
Age, years				
6-9	15.4	15.4	Reference	Reference
10-12	40.8	40.8	1.00 -	1.04 (0.97-1.11)
13-15	35.7	35.7	1.00 -	1.05 (0.98-1.13)
16-18	8.2	8.2	1.00 -	1.00 (0.91-1.10)
BMI status				
Normal weight	84.5	68.4	Reference	Reference
Overweight	9.5	13.7	1.79 (1.67-1.91)	1.77 (1.66-1.90)
Obesity	6.1	17.9	3.65 (3.39-3.93)	3.45 (3.20-3.72)
p for trend			<0.0001	<0.0001
TCOL, mg/dL				
<200	90.0	85.7	Reference	Reference
200-249	8.6	11.8	1.44 (1.34-1.54)	1.22 (1.14-1.32)
≥250	1.4	2.5	1.96 (1.67-2.30)	1.58 (1.34-1.87)
p for trend			<0.0001	<0.0001
Albumin, mg/dL				
<4.5	63.5	59.7	Reference	Reference
4.5-4.9	31.2	34.3	1.17 (1.12-1.23)	1.16 (1.10-1.21)
≥5.0	5.4	6.1	1.20 (1.09-1.31)	1.18 (1.07-1.30)
p for trend			<0.0001	<0.0001
BUN, mg/dL				
<23	99.1	98.9	Reference	Reference
≥23	0.9	1.1	1.22 (0.99-1.50)	1.12 (0.90-1.39)
GFR, ml/min/1.73 m^2				
≥60	83.4	81.5	Reference	Reference
<60	16.6	18.5	1.15 (1.09-1.21)	1.15 (1.02-1.31)

BMI, body mass index; *TCOL*, total cholesterol; *BUN*, blood urea nitrogen; *GFR*, glomerular filtration rate; Missing data: 143 in BMI, 287 in TCOL, 286 in albumin, 278 in BUN, and 282 in creatinine

Table 2-4. Hypertension risk in relation with body mass index among children with hematuria, proteinuria, and glucosuria

	Hematuria	Proteinuria	Glucosuria
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Number	13434	20912	750
BMI status			
Normal weight	Reference	Reference	Reference
Overweight	1.75 (1.58-1.94)	1.76 (1.60-1.93)	2.41 (1.35-4.29)
Obesity	3.21 (2.87-3.58)	3.64 (3.26-4.06)	3.98 (2.66-5.94)

BMI, body mass index.

Normal weight: body mass index <85 percentile; over weight: body mass index = 85-94 percentile; obesity: body mass index ≥95 percentile.

Table 2-5. Odds ratios and 95% confidence intervals for risk of hypertension associated with body mass index by sex, age, total cholesterol, blood urea nitrogen, and creatinine and albumin

	Status of body mass index		
	Normal weight aOR (95% CI)	Overweight aOR (95% CI)	Obesity aOR (95% CI)
Sex			
Girls	Reference	1.82 (1.66-1.98)	3.54 (3.20-3.92)
Boys	0.98 (0.93-1.03)	1.66 (1.49-1.84)	3.47 (3.11-3.87)
Age, years			
6-9	Reference	1.64 (1.40-1.93)	3.06 (2.57-3.65)
10-12	1.02 (0.95-1.10)	1.75 (1.56-1.96)	3.28 (2.89-3.72)
13-15	1.01 (0.93-1.09)	1.78 (1.56-2.04)	3.99 (3.46-4.60)
16-18	0.88 (0.79-0.98)	2.31 (1.78-3.01)	4.55 (3.51-5.90)
TCOL, mg/dL			
<200	Reference	1.75 (1.63-1.88)	3.42 (3.15-3.71)
200-249	1.21 (1.11-1.32)	2.16 (1.78-2.63)	5.17 (4.29-6.21)
≥250	1.54 (1.26-1.88)	4.02 (2.56-6.32)	6.15 (4.12-9.18)
Albumin, mg/dL			
<5.0	Reference	1.78 (1.66-1.90)	3.59 (3.33-3.88)
≥5.0	1.15 1.04-1.28	1.91 (1.46-2.50)	3.26 (2.45-4.35)
BUN, mg/dL			
<23	Reference	1.77 (1.65-1.89)	3.55 (3.29-3.83)
≥23	1.13 0.90-1.43	2.17 (1.05-4.48)	3.66 (1.74-7.73)
GFR, ml/min/1.73 m^2			
≥ 60	Reference	1.79 (1.67-1.92)	3.53 (3.27-3.81)
<60	1.18 (1.03-1.36)	1.47 (1.03-2.11)	5.14 (3.43-7.72)

TCOL, total cholesterol; *BUN*, blood urea nitrogen; *GFR*, glomerular filtration rate.

Table 3-1. General characteristics of school children by birth weight category

	Birth weight, g					
	< 2500	2500-2999	3000-3499	3500-3999	≥ 4000	p-value
Number	3904	16922	40829	22387	5626	
Age, years	11.7 ± 2.8	11.6 ± 2.7	11.9 ± 2.7	12.0 ± 2.7	12.1 ± 2.6	<0.0001
Body mass index, kg/m^2	18.6 ± 3.8	18.5 ± 3.6	18.8 ± 3.57	19.2 ± 3.7	20.0 ± 4.0	<0.0001
Systolic blood pressure, mmHg	107.1 ± 14.7	106.6 ± 14.0	107.5 ± 14.1	108.3 ± 14.2	109.7 ± 14.5	<0.0001
Diastolic blood pressure, mmHg	67.5 ± 11.0	67.1 ± 10.5	67.7 ± 10.5	68.1 ± 10.6	68.9 ± 10.7	<0.0001
Fasting glucose, mg/dL	89.7 ± 29.1	87.3 ± 21.6	87.3 ± 21.2	87.9 ± 23.5	91.9 ± 34.4	<0.0001
Total cholesterol, mg/dL	165.6 ± 37.4	164.0 ± 35.7	163.7 ± 34.2	163.6 ± 35.0	164.1 ± 34.9	0.024
Girl, %	68.2	70.0	64.6	56.2	50.9	<0.0001
Obesity, %	3.8	2.9	3.1	3.9	6.1	<0.0001
Hypertension, %	9.1	7.8	8.6	9.4	10.6	<0.0001
Fasting glucose ≥100 mg/dL, %	6.4	5.0	4.5	4.8	7.9	<0.0001
Total cholesterol ≥200 mg/dL, %	12.6	11.7	11.7	11.7	12.0	0.60

Values are mean ± SD otherwise are percents.

Continuous anthropometrics and blood profiles were analyzed by ANOVA; categorical anthropometric and blood profiles were analyzed by Chi-square tests.

Obesity: body mass index ≥ 27 kg/m^2.

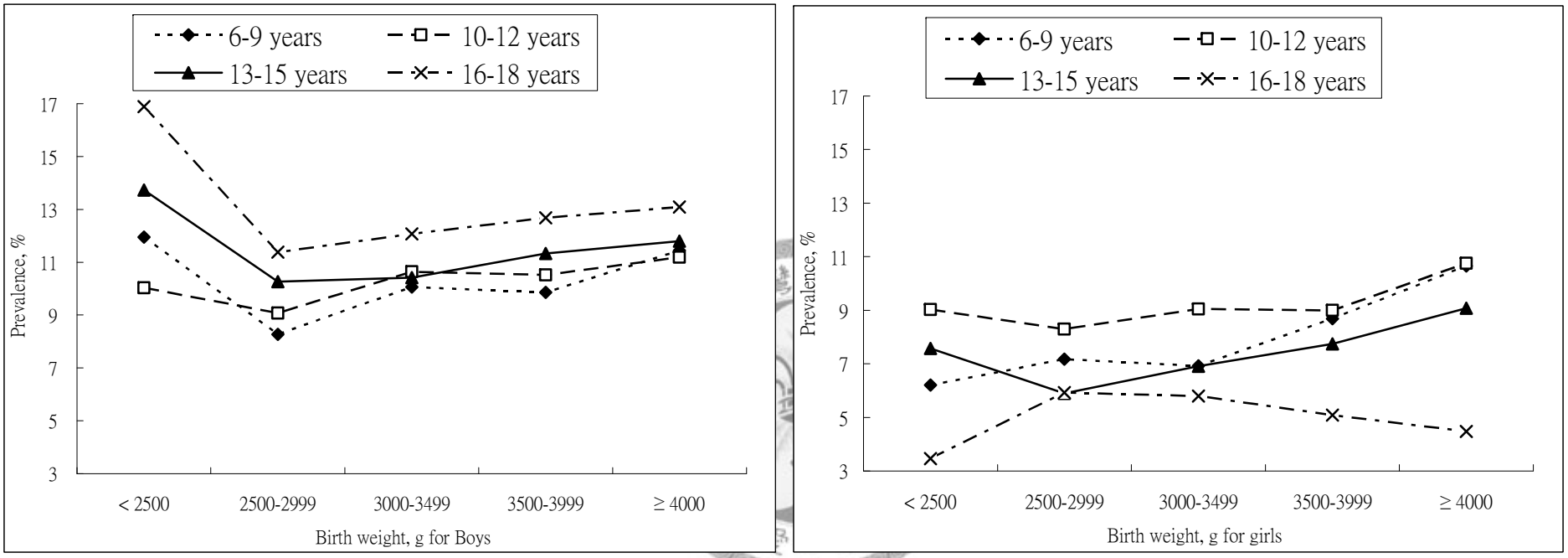


Figure. 3-1. Prevalence of hypertension among school girls and boys by age and birth weight category

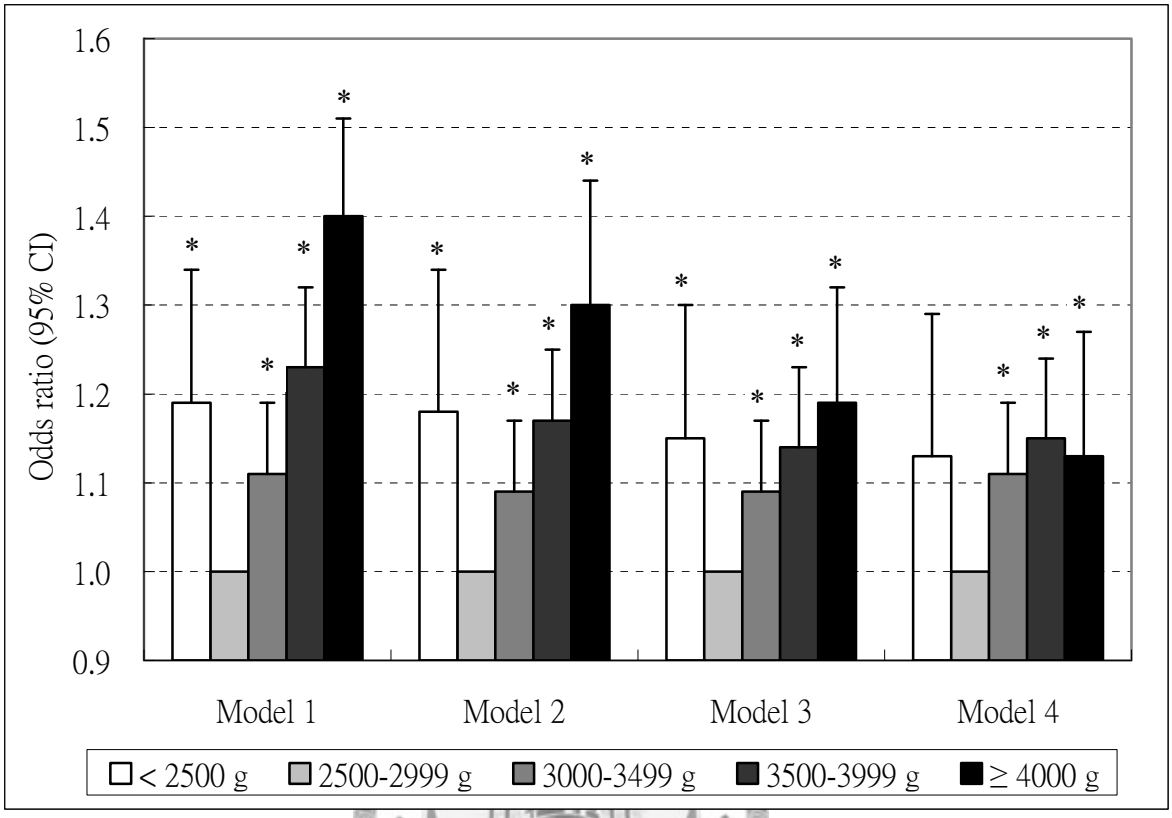


Figure 3-2. Risk of hypertension by birth weight category among school children

*p<0.05

Model 1: unadjusted

Model 2: adjusted for age and sex

Model 3: adjusted for age, sex, and body mass index

Model 4: adjusted for model 3 variables, and fasting glucose and total cholesterol

Table 3-2. Risk of hypertension associated with birth weight in non-obese and obese children measured using multivariate logistic regression models

	Non-Obesity	Obesity	Overall
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Sex			
Girls	1.00 (reference)	1.00 (reference)	1.00 (reference)
Boys	1.40 (1.33-1.48)	1.59 (1.35-1.88)	1.44 (1.37-1.52)
Age, years			
6-9	1.00 (reference)	1.00 (reference)	1.00 (reference)
10-12	1.15 (1.06-1.25)	0.87 (0.56-1.35)	0.94 (0.87-1.02)
13-15	0.88 (0.81-0.95)	0.66 (0.43-0.99)	0.64 (0.59-0.70)
16-18	0.73 (0.65-0.81)	0.60 (0.39-0.94)	0.51 (0.45-0.56)
Birth weight, g			
< 2500	1.10 (0.96-1.27)	1.10 (0.72-1.67)	1.11 (0.96-1.27)
2500-2999	1.00 (reference)	1.00 (reference)	1.00 (reference)
3000-3499	1.10 (1.02-1.19)	1.20 (0.95-1.52)	1.09 (1.01-1.17)
3500-3999	1.15 (1.06-1.25)	1.18 (0.92-1.51)	1.09 (1.01-1.18)
≥ 4000	1.19 (1.05-1.34)	0.88 (0.64-1.21)	1.02 (0.90-1.14)
BMI, kg/m^2			
Underweight			1.00 (reference)
Normal weight			1.89 (1.78-2.01)
Overweight			4.20 (3.79-4.64)
Obesity			9.84 (8.93-10.8)

All models were adjusted for fasting glucose, total cholesterol, albumin, blood urea nitrogen, and creatinine.

BMI: body mass index.

Table 3-3. Risk of hypertension with per 1 kg increase of birth weight

	Per 1 kg increase of birth weight
	OR (95% CI)
All[†]	1.07 (1.02-1.13)
Obese students[‡]	0.96 (0.83-1.10)
Non-obese students[‡]	1.09 (1.03-1.16)

[†]Adjusted for age, sex, body mass index, total cholesterol, fasting glucose, albumin, blood urea nitrogen, and creatinine

[‡]Adjusted all variables except body mass index

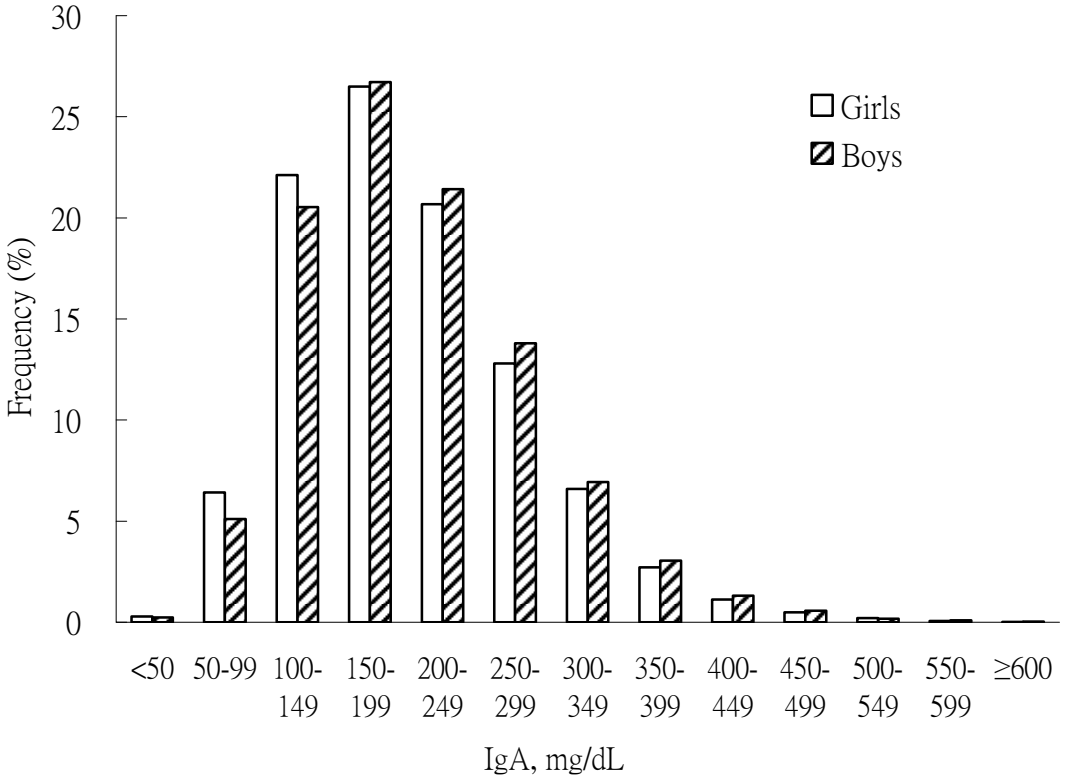


Figure 4-1. Percentage distributions of serum IgA concentrations by sex among school children

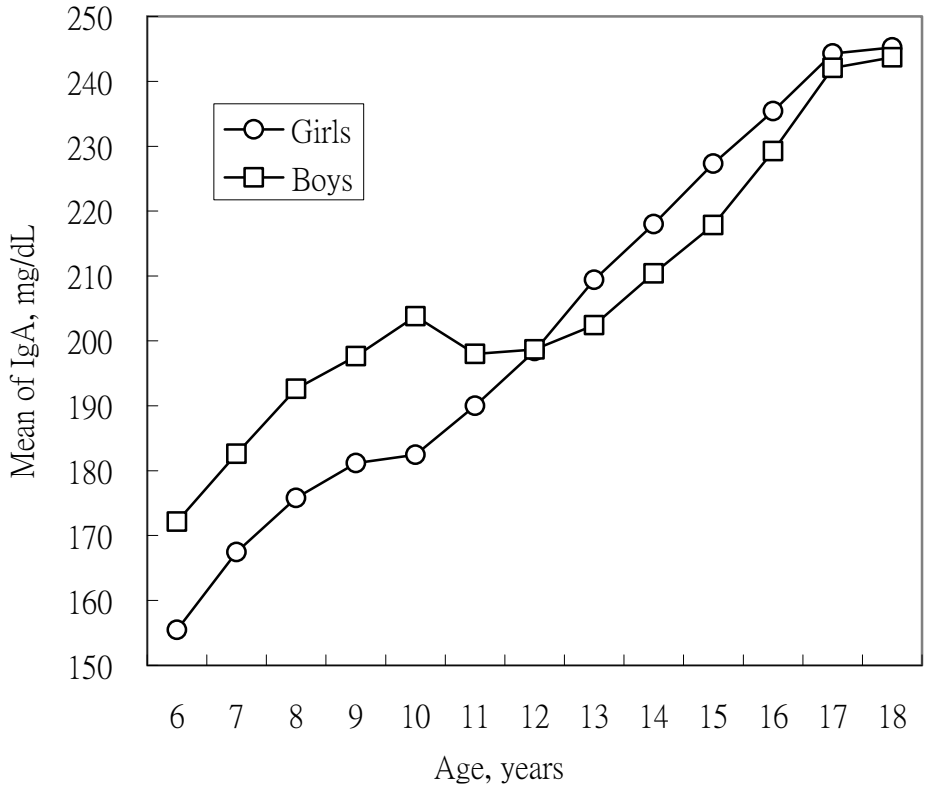


Figure 4-2. The age-specific mean IgA levels by sex in school children

Table 4-1. Distribution of anthropometrics and biomarkers by IgA decile among school children

IgA deciles	1	2	3	4	5	6	7	8	9	10
	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD
Number	9164	9218	9306	9157	9265	9012	9510	9326	9242	9314
Median IgA, mg/dL	94	124	144	162	181	200	222	249	284	348
Age, years	10.9± 2.8	11.3± 2.8	11.6± 2.7	11.8± 2.7	12.0± 2.7	12.2± 2.7	12.4± 2.7	12.6± 2.7	12.7± 2.7	13.2± 2.6
BMI, kg/m^2	18.3± 3.3	18.5± 3.3	18.7± 3.5	18.7± 3.4	19.0± 3.6	19.1± 3.6	19.2± 3.7	19.3± 3.8	19.5± 4.0	20.1± 4.4
SBP, mmHg	105.1± 14.0	106.4± 14.0	107.0± 14.1	107.4± 14.0	108.2± 13.7	108.4± 14.0	108.8± 14.1	108.9± 14.0	109.5± 14.4	110.8± 14.
DBP, mmHg	65.8± 10.5	66.7± 10.5	67.3± 10.4	67.6± 10.4	68.1± 10.4	68.2± 10.5	68.5± 10.5	68.7± 10.6	69.1± 10.6	70.0± 10.
FG, mg/dL	85.7± 19.1	85.7± 18.8	86.5± 20.0	86.8± 23.9	87.0± 23.3	87.9± 25.7	88.7± 27.4	89.2± 30.0	89.8± 32.6	94.4± 46.
TCOL, mg/dL	164.3± 38.9	163.3± 35.5	164.0± 35.4	163.9± 35.6	163.4± 35.7	163.1± 34.8	163.1± 35.5	162.9± 35.0	162.6± 35.6	165.7± 39.
Girls, %	66.7	64.4	63.2	63.2	61.2	61.7	61.1	61.3	60.9	60.5
Obesity, %	1.9	2.3	2.8	2.5	3.3	3.6	3.7	4.3	5.2	7.6
HTN, %	7.5	8.0	8.2	8.8	9.1	9.0	9.0	8.7	9.5	10.8
IFG, %	11.0	11.6	13.0	12.1	13.6	14.1	15.1	15.5	16.0	19.0
High TCOL, %	12.1	10.7	11.0	11.3	10.8	11.5	10.8	11.6	11.4	14.3

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FG, fasting glucose; TCOL, total cholesterol; HTN, hypertension; IFG, impaired fasting glucose.

*$p<0.0001$ in ANOVA and Chi-square tests.

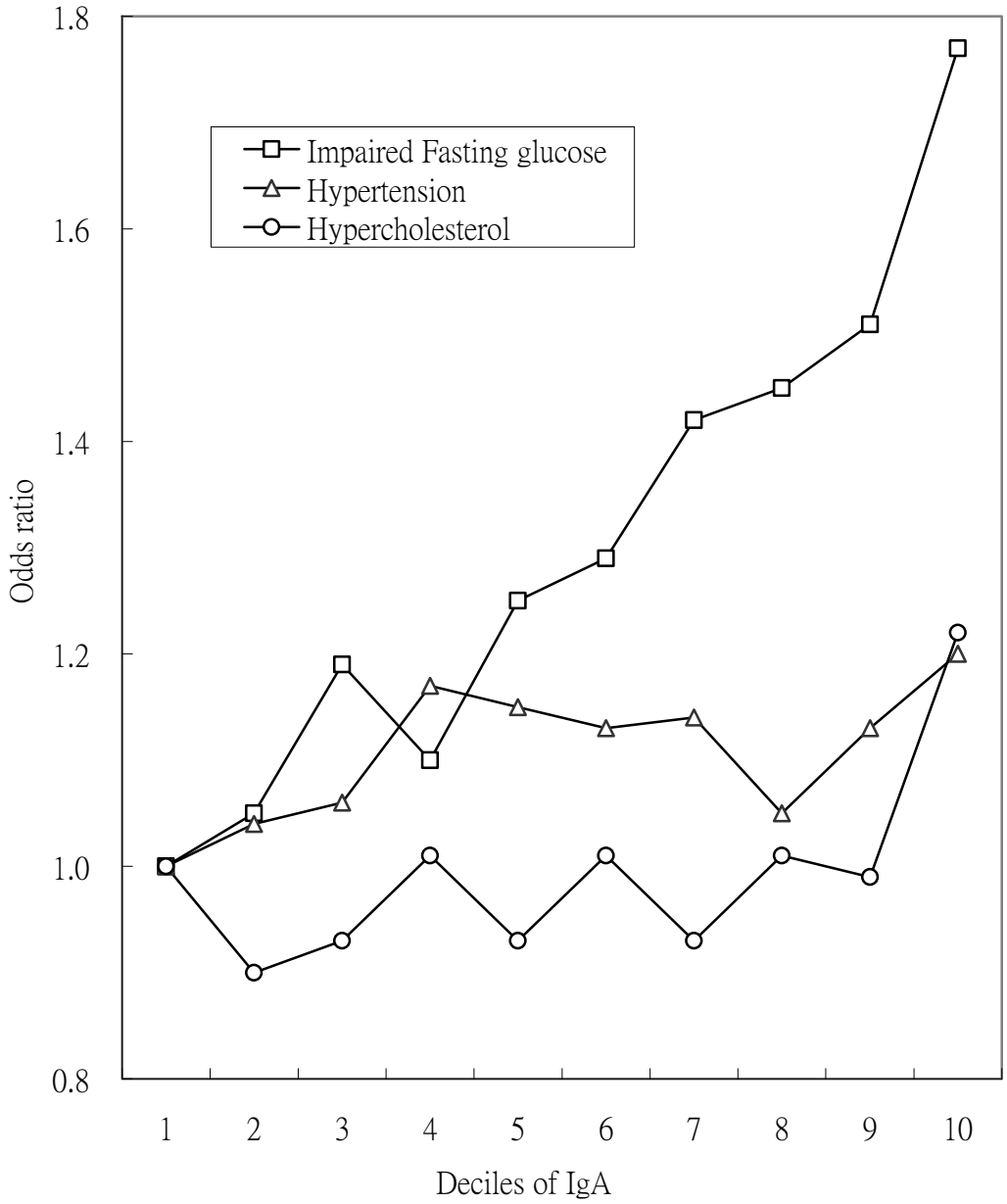


Figure 4-3. Odds ratios of impaired fasting glucose, hypertension and hypercholesterol in association with IgA in school children controlling for age, sex, and obesity

Table 4-2. Risk of impaired fasting glucose by obesity status associated with IgA

	Impaired fasting glucose	
	Non-obese	Obese
Decile IgA	OR (95% CI)	OR (95% CI)
1	1.00 (reference)	1.00 (reference)
2	1.05 (0.96-1.16)	1.03 (0.61-1.73)
3	1.20 (1.09-1.31)	1.13 (0.69-1.86)
4	1.10 (1.00-1.21)	1.01 (0.61-1.68)
5	1.25 (1.14-1.38)	1.25 (0.78-2.00)
6	1.29 (1.18-1.42)	1.29 (0.81-2.05)
7	1.41 (1.29-1.54)	1.75 (1.11-2.75)
8	1.43 (1.31-1.57)	1.91 (1.23-2.98)
9	1.50 (1.36-1.64)	1.83 (1.19-2.83)
10	1.69 (1.54-1.85)	2.93 (1.93-4.44)
p for trend	<0.0001	<0.0001

There was a strong interaction between IgA levels and obesity ($p<0.0001$)

Table 4-3. Risks of hypertension, hypercholesterol, and impaired fasting glucose with per 100 mg/dL increase of IgA

	Per 100 mg/dL increase of IgA	
	OR (95% CI)	OR (95% CI)
Risk of hypertension	1.12 (1.09-1.15) [¶]	1.05 (1.02-1.08) [†]
Risk of hypercholesterol	1.14 (1.11-1.17) [¶]	1.09 (1.06-1.11) [‡]
Risk of impaired fasting glucose	1.26 (1.24-1.29) [¶]	1.23 (1.20-1.26) [*]

[¶]adjusted for age and sex

[†]Adjusted for age, sex, obesity, hypercholesterol, and impaired fasting glucose

[‡]Adjusted for age, sex, obesity, hypertension, and impaired fasting glucose

[*]Adjusted for age, sex, obesity, hypertension, and hypercholesterol

Table 4-4. Risk of impaired fasting glucose associated with IgA among students with hematuria and proteinuria

	Risk of impaired fasting glucose	
	Hematuria†	Proteinuria†
Decile IgA	OR (95% CI)	OR (95% CI)
1	1.00 (reference)	1.00 (reference)
2	1.15 (0.99-1.34)	1.00 (0.88-1.13)
3	1.36 (1.17-1.57)	1.09 (0.96-1.23)
4	1.18 (1.01-1.38)	1.02 (0.90-1.15)
5	1.34 (1.15-1.56)	1.16 (1.02-1.30)
6	1.36 (1.17-1.58)	1.18 (1.05-1.34)
7	1.42 (1.23-1.64)	1.32 (1.17-1.49)
8	1.47 (1.27-1.70)	1.30 (1.15-1.46)
9	1.61 (1.39-1.87)	1.29 (1.15-1.46)
10	1.61 (1.39-1.87)	1.44 (1.28-1.63)
p for trend	<0.0001	<0.0001

†adjusted for sex, age, obesity, hypertension, and hypercholesterol

Table 5-1. Comparison in baseline childhood measures between children with hypertension and with no hypertension at baseline

		Childhood baseline hypertension		
	Total	No	Yes	
Baseline childhood measures	Mean ± SD	Mean ± SD	Mean ± SD	p-value
Number	988	641	347	
Age, years	12.2 ± 2.8	12.2 ± 2.8	12.1 ± 2.8	0.65
Body mass index, kg/m^2	19.1 ± 4.0	18.2 ± 3.1	20.8 ± 4.9	<0.0001
Systolic blood pressure, mmHg	111.4 ± 17.2	102.9 ± 11.3	127.1 ± 15.2	<0.0001
Diastolic blood pressure, mmHg	71.8 ± 13.7	64.4 ± 8.6	85.3 ± 10.7	<0.0001
Fasting glucose, mg/dL	85.2 ± 20.0	83.7 ± 12.1	87.8 ± 29.3	0.015
Total cholesterol, mg/dL	162.3 ± 35.7	160.2 ± 31.2	166.2 ± 42.6	0.022
Obesity, %	9.2	3.5	19.7	<0.0001
Hyperglycemia, %	10.1	8.7	12.7	0.05
Hypercholesterol, %	10.8	9.2	13.8	0.025

Hypercholesterol: total cholesterol ≥200 mg/dL; Hyperglycemia: fasting glucose ≥100 mg/dL

Table 5-2. Lifestyle, anthropometrics, and biomarkers of study participants at follow-up measures by baseline childhood hypertension status

		Childhood baseline hypertension		
	Total	No	Yes	
Current measures	Mean ± SD	Mean ± SD	Mean ± SD	p-value
Number	988	641	347	
Age, years	21.5 ± 3.4	21.9 ± 3.3	20.9 ± 3.4	<0.0001
Body mass index, kg/m^2	21.8 ± 4.1	21.0 ± 3.2	23.3 ± 5.0	<0.0001
Waist circumference, cm	71.4 ± 11.4	69.2 ± 9.1	75.4 ± 13.9	<0.0001
Systolic blood pressure, mmHg	108.2 ± 14.4	105.6 ± 12.2	113.0 ± 16.7	<0.0001
Diastolic blood pressure, mmHg	67.9 ± 11.4	65.8 ± 9.7	71.9 ± 13.0	<0.0001
high-density lipoprotein cholesterol, mg/dL	50.6 ± 10.2	51.8 ± 10.0	48.4 ± 10.4	<0.0001
Triglyceride, mg/dL	84.0 ± 72.5	78.0 ± 40.4	95.1 ± 108.5	0.005
Log triglyceride	1.86 ± 0.20	1.85 ± 0.18	1.89 ± 0.24	0.015
Fasting glucose, mg/dL	85.8 ± 19.3	83.8 ± 9.8	89.6 ± 29.5	0.0004
Boys, %	38.9	36.7	42.9	0.053
Smoking, %	12.6	13.5	10.9	0.24
Alcohol drinking, %	9.5	11.0	6.5	0.022
Abdominal Obesity, %	10.4	5.1	20.2	<0.0001
High blood pressure, %	10.5	5.6	19.6	<0.0001
Low high-density lipoprotein cholesterol, %	32.2	26.8	42.1	<0.0001
Hypertriglyceridemia, %	6.9	5.2	10.1	0.003
Hyperglycemia, %	3.7	2.0	6.9	0.0001

Abdominal obesity: waist circumference ≥ 90 cm in men and ≥ 80 cm in women; high blood pressure: systolic blood pressure ≥

130 mmHg or diastolic blood pressure ≥ 85 mmHg; low high-density lipoprotein cholesterol: high-density lipoprotein cholesterol < 40 mg/dL in men and high-density lipoprotein cholesterol < 50 mg/dL in women; hypertriglyceridemia: triglyceride ≥150 mg/dL; Hyperglycemia: fasting glucose ≥100 mg/dL

Table 5-3. Anthropometrics and blood pressures at follow-up measures by sex and baseline childhood hypertension among study participants

	Childhood hypertension		
	No	Yes	
	Mean ± SD	Mean ± SD	p-value
Male (N=384)			
Number	235	149	
Age, years	21.8 ± 3.1	21.4 ± 3.5	0.23
BMI, kg/m^2	21.9 ± 3.4	24.7 ± 5.4	<0.0001
Waist, cm	75.0 ± 9.2	81.3 ± 13.1	<0.0001
SBP, mmHg	112.8 ± 12.2	121.1 ± 16.5	<0.0001
DBP, mmHg	69.7 ± 10.0	77.1 ± 13.2	<0.0001
Female (N=604)			
Number	406	198	
Age, years	21.9 ± 3.4	20.5 ± 3.3	<0.0001
BMI, kg/m^2	20.5 ± 3.0	22.3 ± 4.4	<0.0001
Waist, cm	65.8 ± 7.2	70.9 ± 12.9	<0.0001
SBP, mmHg	101.4 ± 10.2	106.9 ± 14.2	<0.0001
DBP, mmHg	63.5 ± 8.7	68.1 ± 11.5	<0.0001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 5-4. Age- and sex-adjusted Spearman correlation coefficients between childhood blood pressure and follow-up measures by childhood hypertension

	Childhood hypertension			
	No (N = 641)		Yes (N = 347)	
Current	SBP, mmHg	DBP, mmHg	SBP, mmHg	DBP, mmHg
Waist circumference, cm	0.177***	0.113*	0.150*	0.059
SBP, mmHg	0.204***	0.151***	0.219***	0.089
DBP, mmHg	0.141**	0.128*	0.090	0.221***
HDL-C, mg/dL	- 0.012	0.010	0.022	- 0.030
Triglyceride, mg/dL	0.020	0.001	0.064	- 0.064
Fasting glucose, mg/dL	- 0.085*	- 0.084*	0.050	0.118*

*p<0.05, **p<0.001, ***p<0.0001

HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol.

Table 5-5. Baseline blood pressure by metabolic component at follow-up measures of study participants

		Baseline childhood blood pressure			
		SBP, mmHg		DBP, mmHg	
	n	Mean ± SD	p-value	Mean ± SD	p-value
Abdominal obesity			<0.0001		<0.0001
No	885	109.9 ± 16.4		70.7 ± 13.1	
Yes	103	123.8 ± 19.2		80.8 ± 15.2	
High blood pressure			<0.0001		<0.0001
No	884	109.9 ± 16.6		70.8 ± 13.1	
Yes	104	123.7 ± 17.8		80.2 ± 15.8	
Low HDL-C			0.24		0.009
No	670	110.9 ± 17.1		71.0 ± 13.3	
Yes	318	112.3 ± 17.4		73.4 ± 14.4	
Hypertriglyceridemia			0.0001		0.032
No	920	110.8 ± 17.0		71.5 ± 13.4	
Yes	68	119.1 ± 18.3		75.9 ± 16.4	
Hyperglycemia			0.008		0.019
No	951	111.0 ± 16.9		71.5 ± 13.4	
Yes	37	121.8 ± 23.2		79.3 ± 19.2	
Metabolic syndrome			<0.0001		0.004
No	949	110.7 ± 16.8		71.4 ± 13.3	
Yes	39	127.7 ± 20.2		80.9 ± 19.2	

SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; abdominal obesity: waist circumference ≥ 90 cm in men and ≥ 80 cm in women; high blood pressure: systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg; low HDL-C: high-density lipoprotein cholesterol < 40 mg/dL in men and high-density lipoprotein cholesterol < 50 mg/dL in women; Hypertriglyceridemia: triglyceride ≥150 mg/dL; Hyperglycemia: fasting glucose ≥100 mg/dL; Metabolic syndrome: at least 3 of the following 5 criteria: Abdominal obesity, high blood pressure, low high-density lipoprotein cholesterol, hypertriglyceridemia, and hyperglycemia.

Table 5-6. Comparison in baseline blood pressure between metabolic abnormalities by childhood hypertension status

	No childhood hypertension (n = 641)					With childhood hypertension (n = 347)				
		Childhood SBP, mmHg		Childhood DBP, mmHg			Childhood SBP, mmHg		Childhood DBP, mmHg	
Follow-up measures	n	Mean ± SD	p	Mean ± SD	p	n	Mean ± SD	p	Mean ± SD	p
Abdominal obesity			0.17		0.19			0.001		0.07
No	608	102.7 ± 11.4		64.3 ± 8.6		277	125.7 ± 14.6		84.7 ± 10.3	
Yes	33	105.5 ± 9.5		66.4 ± 9.7		70	132.4 ± 16.5		87.6 ± 12.3	
High blood pressure			<0.0001		0.18			0.028		0.15
No	605	102.4 ± 11.1		64.3 ± 8.5		279	126.2 ± 14.8		84.8 ± 10.0	
Yes	36	110.5 ± 12.4		66.9 ± 11.1		68	130.7 ± 16.3		87.3 ± 13.2	
Low HDL-C			0.15		0.09			0.013		0.81
No	469	103.3 ± 11.3		64.8 ± 8.5		201	128.8 ± 15.1		85.4 ± 11.0	
Yes	172	101.8 ± 11.1		63.5 ± 8.9		146	124.7 ± 15.2		85.1 ± 10.4	
Hypertriglyceridemia			0.32		0.99			0.006		0.41
No	608	102.8 ± 11.2		64.4 ± 8.5		312	126.4 ± 15.5		85.1 ± 10.5	
Yes	33	104.8 ± 12.4		64.4 ± 11.4		35	132.5 ± 11.5		86.7 ± 12.7	
Hyperglycemia			0.09		0.030			0.009		0.023
No	628	103.0 ± 11.3		64.6 ± 8.6		323	126.5 ± 15.0		84.9 ± 10.5	
Yes	13	97.6 ± 11.9		59.3 ± 10.7		24	134.8 ± 16.1		90.1 ± 12.9	
Metabolic syndrome			0.90		0.05			0.003		0.42
No	632	102.9 ± 11.3		64.5 ± 8.6		317	126.3 ± 15.0		85.1 ± 10.2	
Yes	9	103.3 ± 12.6		58.9 ± 11.9		30	135.0 ± 15.8		87.5 ± 15.7	

SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol

Table 5-6-2. Comparison in baseline blood pressure between metabolic abnormalities by childhood hypertension

	Childhood SBP, mmHg						Childhood DBP, mmHg					
	No childhood HTN			Have childhood HTN			No childhood HTN			Have childhood HTN		
Follow-up measures	n	Mean ± SD	p	n	Mean ± SD	p	n	Mean ± SD	p	Mean ± SD	p	
Abdominal obesity			0.17			0.001			0.19		0.07	
No	608	102.7 ± 11.4		277	125.7 ± 14.6			64.3 ± 8.6		84.7 ± 10.3		
Yes	33	105.5 ± 9.5		70	132.4 ± 16.5			66.4 ± 9.7		87.6 ± 12.3		
Difference		**2.8**			**6.7**			**2.0**		**2.9**		
High blood pressure			<0.0001			0.028			0.18		0.15	
No	605	102.4 ± 11.1		279	126.2 ± 14.8			64.3 ± 8.5		84.8 ± 10.0		
Yes	36	110.5 ± 12.4		68	130.7 ± 16.3			66.9 ± 11.1		87.3 ± 13.2		
Difference		**8.1**			**4.5**			**2.6**		**2.5**		
Low HDL-C			0.15			0.013			0.09		0.81	
No	469	103.3 ± 11.3		201	128.8 ± 15.1			64.8 ± 8.5		85.4 ± 11.0		
Yes	172	101.8 ± 11.1		146	124.7 ± 15.2			63.5 ± 8.9		85.1 ± 10.4		
Difference		**-1.5**			**-4.1**			**1.3**		**-0.3**		
Hypertriglyceridemia			0.32			0.006			0.99		0.41	
No	608	102.8 ± 11.2		312	126.4 ± 15.5			64.4 ± 8.5		85.1 ± 10.5		
Yes	33	104.8 ± 12.4		35	132.5 ± 11.5			64.4 ± 11.4		86.7 ± 12.7		
Difference		**2.0**			**6.1**			**0.0**		**1.6**		
Hyperglycemia			0.09			0.009			0.030		0.023	
No	628	103.0 ± 11.3		323	126.5 ± 15.0			64.6 ± 8.6		84.9 ± 10.5		
Yes	13	97.6 ± 11.9		24	134.8 ± 16.1			59.3 ± 10.7		90.1 ± 12.9		

Difference		**-5.4**		**7.4**		**-5.2**		**5.2**
Metabolic syndrome			0.90		0.003		0.05	0.42
No	632	102.9 ± 11.3	317	126.3 ± 15.0		64.5 ± 8.6		85.1 ± 10.2
Yes	9	103.3 ± 12.6	30	135.0 ± 15.8		58.9 ± 11.9		87.5 ± 15.7
Difference		**0.5**		**8.7**		**-5.6**		**2.4**

SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; HDL-C, high-density lipoprotein cholesterol

Table 5-7. Childhood blood pressure between number of components of metabolic syndrome

		Childhood blood pressure			
		SBP, mmHg		DBP, mmHg	
Metabolic syndrome	n	Mean ± SD	p-value*	Mean ± SD	p-value*
Number of components			<0.0001		<0.0001
0	549	108.9 ± 16.0		69.6 ± 12.4	
1	305	111.2 ± 17.1		72.1 ± 14.1	
2	95	119.6 ± 17.2		79.7 ± 12.7	
3 and more	39	127.7 ± 20.2		80.9 ± 19.2	

*ANOVA

SBP, systolic blood pressure; DBP, diastolic blood pressure; Metabolic syndrome: at least 3 of the following 5 criteria: abdominal obesity, high blood pressure, low high-density lipoprotein cholesterol, hypertriglyceridemia, and hyperglycemia

Table 5-8. Childhood blood pressures at follow-up measures by study group and number of metabolic syndrome components

	Number of metabolic syndrome components				
	0	1	2	3 and more	
Childhood baseline blood pressure	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	p-value
No childhood hypertension					
Number	411	185	36	9	
SBP, mmHg	102.8 ± 11.1	102.1 ± 11.5	107.3 ± 11.5	103.3 ± 12.6	0.06
DBP, mmHg	64.6 ± 8.4	63.5 ± 8.7	68.8 ± 9.4	58.9 ± 11.9	0.004
Have childhood hypertension					
Number	138	120	59	30	
SBP, mmHg	126.9 ± 14.7	125.2 ± 14.8	127.0 ± 15.8	135.0 ± 15.8	0.001
DBP, mmHg	84.3 ± 10.8	85.3 ± 9.8	86.4 ± 9.3	87.5 ± 15.7	0.23
Difference[†]					
SBP, mmHg	24.1[*]	23.1[*]	19.7[*]	31.7[*]	
DBP, mmHg	19.7[*]	21.8[*]	17.6[*]	28.6[*]	

SBP, systolic blood pressure; DBP, diastolic blood pressure; [*] $p<0.0001$

[†]The difference of blood pressure between children and with no hypertension in each category of metabolic syndrome components

Table 5-9. The comparison in childhood baseline blood pressure between children with hypertension and children without hypertension at baseline by numbers of components of metabolic syndrome in early adulthood

	Childhood hypertension				Childhood hypertension			
MS	No	Yes			No	Yes		
components	Mean ± SD	Mean ± SD	Difference	p-value	Mean ± SD	Mean ± SD	Difference	p-value
0	102.8 ± 11.1	126.9 ± 14.7	24.1	<0.0001	64.6 ± 8.4	84.3 ± 10.8	19.7	<0.0001
1	102.1 ± 11.5	125.2 ± 14.8	23.1	<0.0001	63.5 ± 8.7	85.3 ± 9.8	21.8	<0.0001
2	107.3 ± 11.5	127.0 ± 15.8	19.7	<0.0001	68.8 ± 9.4	86.4 ± 9.3	17.6	<0.0001
≥3	103.3 ± 12.6	135.0 ± 15.8	31.7	<0.0001	58.9 ± 11.9	87.5 ± 15.7	28.6	<0.0001
All	102.9 ± 11.3	127.1 ± 15.2	24.2	<0.0001	64.4 ± 8.6	85.3 ± 10.7	20.9	<0.0001

MS, metabolic syndrome

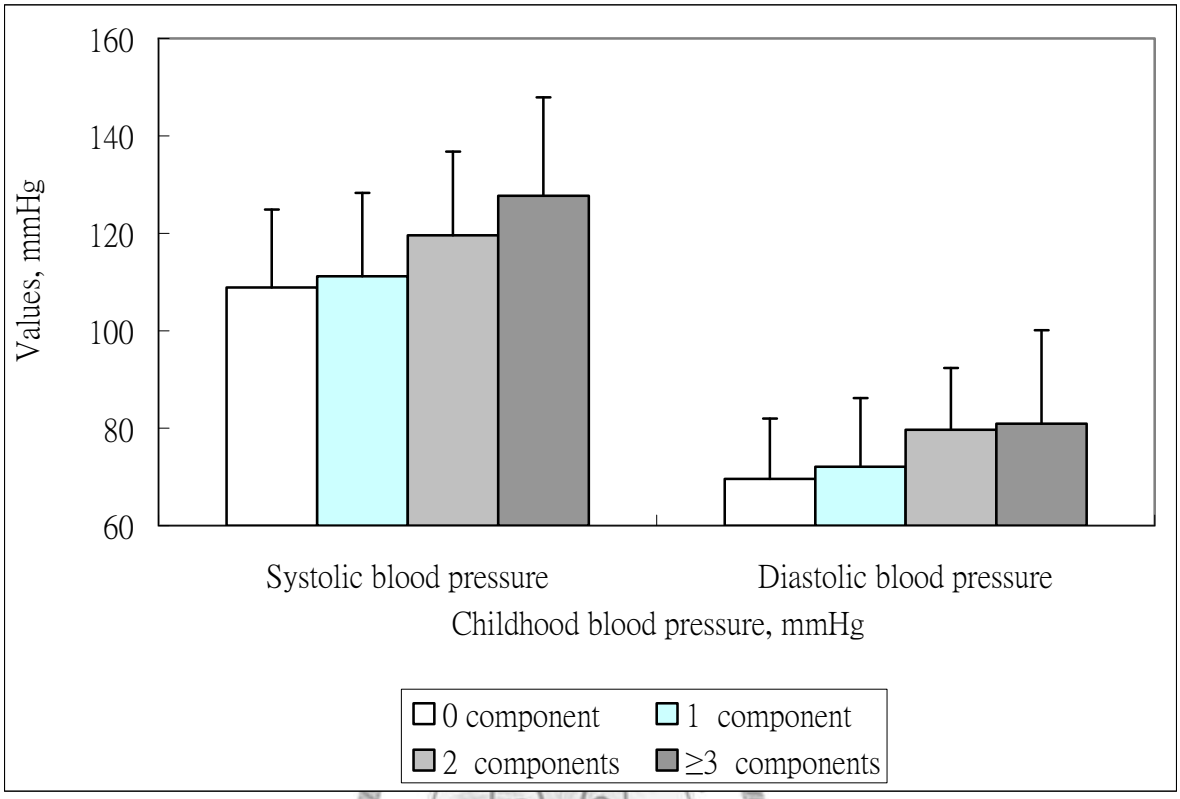
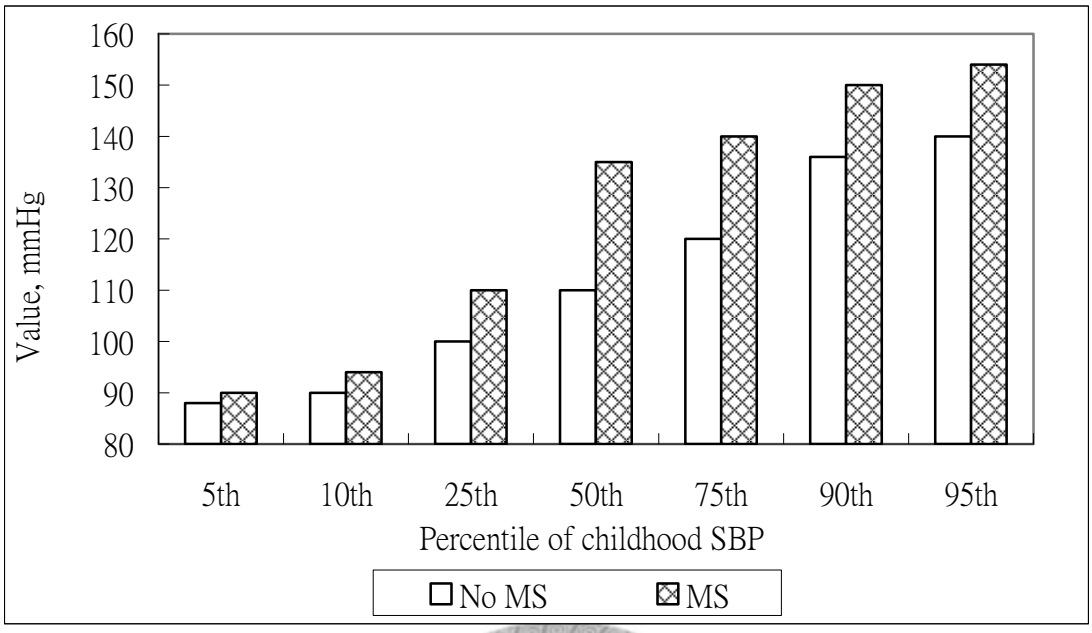


Figure 5-1. Childhood blood pressure at baseline by numbers of metabolic syndrome components



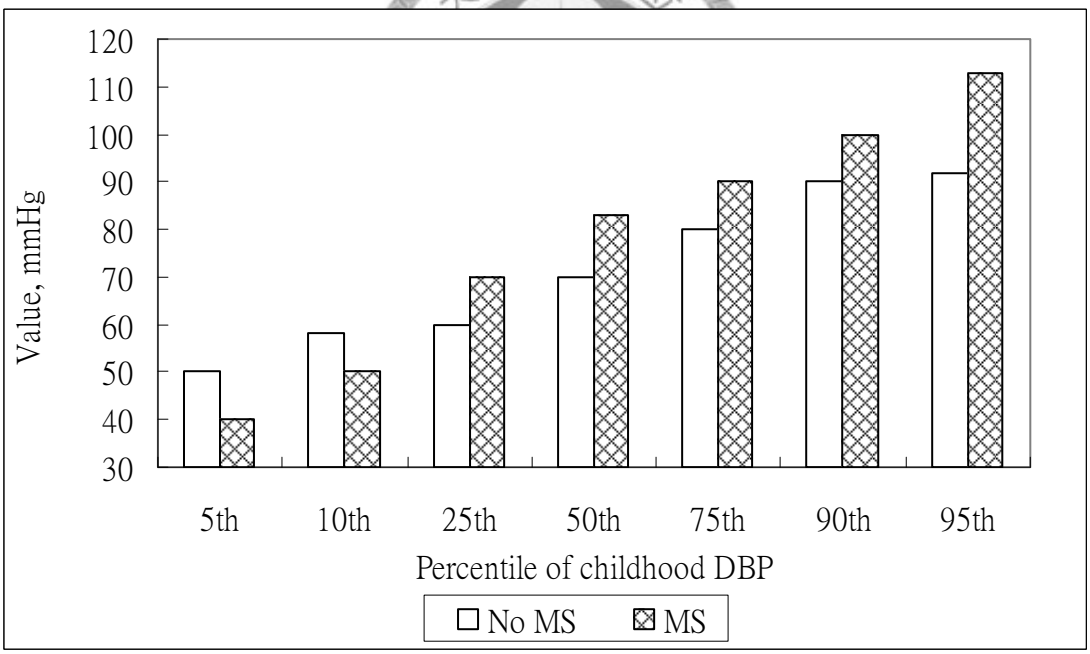
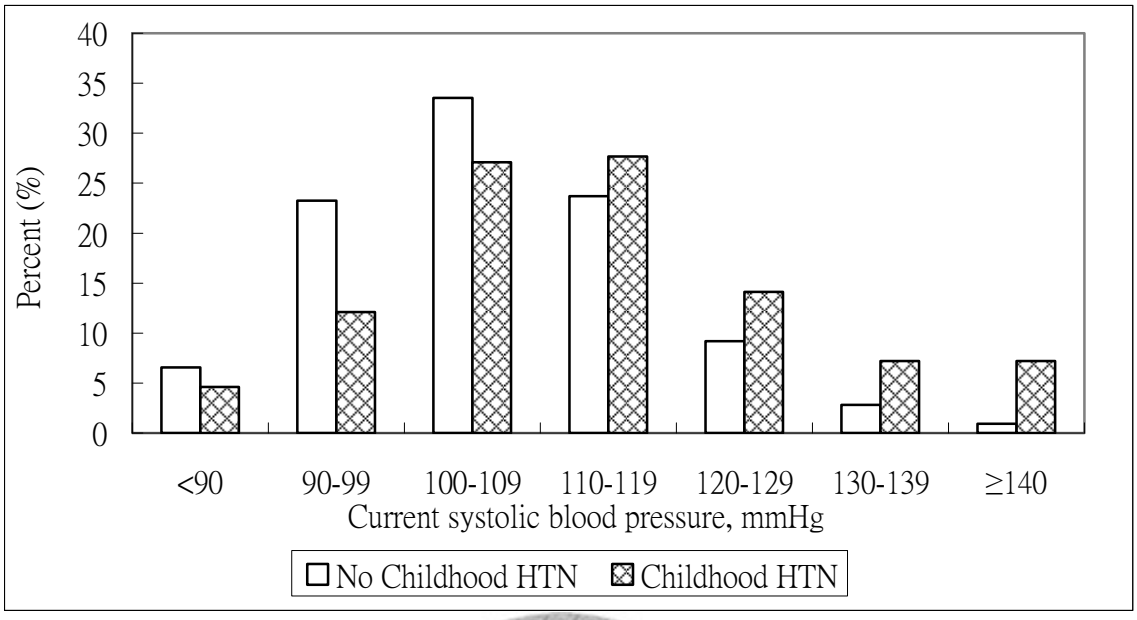


Figure 5-2. Percentile distribution of childhood blood pressure at baseline by metabolic syndrome at follow-up



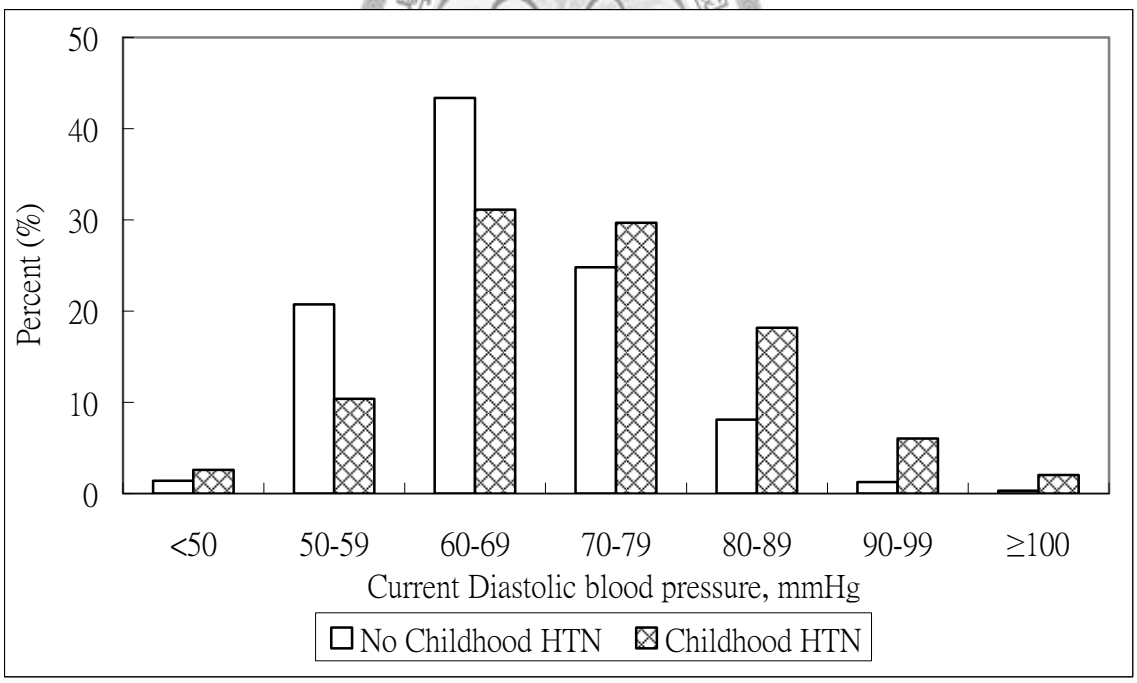


Figure 5-3. Distribution of current blood pressure measured at the follow-up study by childhood hypertension

Table 5-10. Odds ratios and 95% confidence intervals of metabolic abnormalities and metabolic syndrome in association with childhood hypertension

Outcome prevalence, %	Childhood HTN		Model 1	Model 2	Model 3	Model 4
	No N=641	Yes N=347	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Abdominal obesity	5.1	20.2	4.92 (3.15-7.67)	5.14 (3.19-8.28)	2.29 (1.15-4.58)	2.33 (1.14-4.78)
High blood pressure	5.6	19.6	4.26 (2.72-6.68)	4.68 (2.90-7.56)	3.69 (2.23-6.09)	4.19 (2.42-7.28)
Low HDL-C	26.8	42.1	2.04 (1.53-2.71)	2.03 (1.51-2.73)	1.62 (1.18-2.22)	1.73 (1.25-2.40)
Hypertriglyceridemia	5.2	10.1	2.07 (1.25-3.42)	2.18 (1.27-3.76)	1.34 (0.73-2.44)	1.42 (0.75-2.71)
Hyperglycemia	2.0	6.9	3.98 (1.98-8.01)	4.62 (2.11-10.1)	2.70 (1.16-6.28)	4.70 (1.62-13.6)
Metabolic syndrome	1.4	8.7	6.91 (3.21-14.8)	11.0 (4.11-29.5)	3.80 (1.24-11.7)	4.20 (1.23-14.3)

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, education, smoking, alcohol drinking, and family history of hypertension

Model 3: adjusted for variables in model 2 plus body mass index

Model 4: adjusted for variables in model 3 plus insulin, uric acid, and high-sensitivity C-reactive protein

Table 5-11. Risks of metabolic abnormalities and metabolic syndrome at follow-up measures among participants with per 5 mmHg increase of baseline childhood systolic blood pressure

	Per 5 mmHg increase of childhood SBP
Metabolic outcomes[†]	OR (95% CI)
Abdominal obesity	1.10 (1.00-1.21)
High blood pressure	1.20 (1.11-1.30)
Low HDL-C	1.02 (0.97-1.07)
Hypertriglyceridemia	1.09 (0.99-1.19)
Hyperglycemia	1.23 (1.08-1.41)
Metabolic syndrome	1.24 (1.06-1.44)

SBP, systolic blood pressure.

[†]Adjusted for age and sex, education, smoking, alcohol drinking, family history of hypertension, body mass index, insulin, uric acid, and high-sensitivity C-reactive protein.

Table 5-12. Risks of metabolic abnormalities and metabolic syndrome at follow-up measures among participants with per 5 mmHg increase of baseline childhood diastolic blood pressure

	Per 5 mmHg increase of childhood DBP
Metabolic outcomes[†]	OR (95% CI)
Abdominal obesity	1.17 (1.02-1.34)
High blood pressure	1.23 (1.12-1.35)
Low HDL-C	1.05 (0.99-1.11)
Hypertriglyceridemia	1.04 (0.93-1.16)
Hyperglycemia	1.18 (1.01-1.37)
Metabolic syndrome	1.04 (0.86-1.26)

DBP, diastolic blood pressure

[†]Adjusted for age and sex, education, smoking, alcohol drinking, family history of hypertension, body mass index, insulin, uric acid, and high-sensitivity C-reactive protein

附錄

1. Liao CC, Su TC, Chien KL, Wang JK, Lin CC, Chiang CC, Lin RS, Lee YT, Sung FC*. Elevated blood pressure, obesity, and hyperlipidemia. J Pediatr 2009; (In Press) [SCI]

Elevated Blood Pressure, Obesity, and Hyperlipidemia

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Objectives To investigate the association of blood pressure elevation with body mass index (BMI) and total cholesterol levels in children who screened positive for proteinuria, glucosuria, and/or hamaturia.

Study design From 1992 to 2000, a mass urine screening program was conducted annually for nearly 3 000 000 students aged 6 to 18 years. Of 99 350 students with positive results on urine tests, further examination found 17 548 students (17.7%) had blood pressure elevation. A case-control analysis was performed with randomly selected subjects with normal blood pressure who were frequency matched by sex and age.

Results The adjusted odds ratio for blood pressure elevation in obese students was 3.45 (95% CI, 3.20-3.72), compared with students of normal weight. The odds ratio for blood pressure elevation increased to 6.15 (95% CI, 4.12-9.18) for students with a total cholesterol level ≥250 mg/dL and obesity, compared with students with a total cholesterol level <200 mg/dL and normal weight.

Conclusion This study found a high prevalence of elevated blood pressure in children with abnormal urinalysis results, with a strong association with BMI and total choleterol level. *(J Pediatr 2009;■:■-■).*

Studies have provided strong evidence for the important role of obesity in the etiology of hypertension in adults[1] and have demonstrated that obesity affects the blood pressure of children as well.[2-7] The prevalence of childhood hypertension[2-5,8] and obesity[9-13] have been increasing in populations worldwide. Studies in Taiwan also have shown increasing trends of obesity in children.[14-17]

The high prevalence of obesity has increased the importance of studying other risk factors associated with hypertension, including hyperlipidemia, diabetes mellitus, and renal function.[18-20] An annual urine screening for glucosuria, proteinuria, and hematuria was conducted from 1992 to 2000 in Taiwan. This screening demonstrated that childhood diabetes mellitus is strongly related to obesity.[18,19] Compared with children with a body mass index (BMI) <50th percentile, children with a BMI ≥95th percentile were 25.9 times more likely to have diabetes mellitus. This study investigated the risk for hypertension associated with BMI and other factors in this population of school children.

Methods

From 1992 to 2000, the Chinese Foundation of Health in Taipei, Taiwan, conducted an annual urine screening campaign for 2 615 000 to 2 932 000 school-age children in grades 1 to 12 in Taiwan. The project details have been described in earlier reports.[18-23] A urine strip (Hemscomistix IV urine strip, Ames Division, Miles Lab, Elkhart, Indiana) was used for the screening. School-age children with positive results on 2 tests for proteinuria, glucosuria, or hematuria underwent a third urine screening test and a general health check-up with the same protocol. The check-up included anthropometric measures, fasting blood tests for total cholesterol (TCOL), albumin, blood urea nitrogen (BUN), serum creatinine (CRE), C3 complement, antistreptolysin O, and blood pressure. For measurement of blood pressure, students were seated with legs uncrossed, and they refrained from speaking. Blood pressure was measured twice with a mercury sphygmonometer and the appropriate size cuff.

Overall, 131 547 students who participated in the general check-up were referred to their physicians for further diagnosis and follow-up care. The original

BMI	Body mass index
BUN	Blood urea nitrogen
CRE	Creatinine
DBP	Diastolic blood pressure
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
SBP	Systolic blood pressure
TCOL	Total cholesterol

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screening program was conducted as a public policy required by the Taiwan Provincial Department of Health and approved by the Provincial Education Board. A letter was sent to parents to explain the program and invite their participation. Return of the urine sample was taken as consent for participating in the program.

In this study, hypertension was defined as systolic blood pressure, diastolic blood pressure, or both greater than or equal to the sex-, age-, and height-percentile-specific 95th percentile blood pressure values.[24] The **Figure** (available at www.jpeds.com) shows the procedure used to identify cases with hypertension and control subjects. After excluding missing data and unreliable identification (n = 3 134), unknown blood pressure (n = 24 561), unknown results of urine test (n = 84), unknown age (n = 3 488), and unknown height (n = 930), 99 350 school-age children were eligible for this study. Of them, 17 548 students (17.7%) had hypertension. Control subjects were randomly selected from school-age children without hypertension frequency matched by sex and age.

According to the criteria of the Taiwan Nutrition and Health Survey,[25] childhood obesity and overweight were defined as students having a BMI greater than or equal to the sex- and age-specific 95th percentile value and between the 85th and 94th percentile values, respectively. The glomerular filtration rate (GFR) was calculated for each child.[26]

First, the means of SBP, DBP, TCOL, albumin, BUN, and CRE levels and GFR were compared, between subjects with hypertension and control subjects by the BMI group. The Kruskal-Wallis test was used to evaluate differences. Comparisons between subjects with hypertension and control subjects were also performed for sex, age, levels of BMI, TCOL, albumin, BUN, and GFR in BMI groups. The categorical outpoints for those variables were TCOL (<200, 200-249, ≥250 mg/dL), albumin (<4.5, 4.5-4.9, ≥5.0 mg/dL), BUN (<23 mg/dL, ≥23 mg/dL), and GFR (<60 mL/min/1.73m^2, ≥60 mL/min/1.73m^2).[27] Odds ratios (ORs) and 95% CI for the risk of hypertension associated with these factors were estimated with logistic regression analysis. Interaction between BMI levels and each co-variate was also calculated. SAS software version 8.0 (SAS Institute, Carey, North Carolina) was used for data analyses, with a 2-sided probability value <.05 considered to be statistically significant.

Results

The mean SBP, DBP, and TCOL levels were consistently higher in subjects with hypertension than in control subjects, significant at a P value ≤.01 (**Table I**; available at www.jpeds.com). The difference for SBP and TCOL, but not DBP, levels are greater for obese subjects than normal weight subjects. The prevalence of stage 2 hypertension was much greater in obese children than normal weight children (22.5% versus 6.0%).

Of 99 350 students, 1503 of them had glucosuria without having hematuria or proteinuria. In our case-control analysis, students with hypertension were more likely to have glucosuria than were students with normal blood pressure (3.1% versus 1.0%, $P < .0001$; data not shown). Students with higher BMI, TCOL levels, and albumin levels and lower GFR were at higher risk for hypertension than control subjects (**Table II**). Elevated blood pressure was 3 times more prevalent in students with obesity than control subjects (17.9% versus 6.1%, $P < .0001$). In the multivariate analysis, BMI had the strongest association with hypertension risk (OR, 3.45; 95% CI, 3.20-3.72), followed by TCOL level. Both BMI and TCOL level had a strong dose-response relationship ($P < .0001$). The OR of hypertension associated with obesity changed slightly when data were analyzed separately for students with hematuria (OR, 3.21; 95% CI, 2.87-3.58), proteinuria (OR, 3.64; 95% CI, 3.26-4.06), and glucosuria (OR, 3.98; 95% CI, 2.66-5.94; **Table III**).

The multivariate logistic regression analysis by BMI strata revealed that the OR for hypertension increased as BMI increased for both girls and boys and in all age groups in a similar pattern (**Table IV**). The older children had a greater association between BMI and hypertension risk compared with younger children. When children aged 6 to 9 years with normal weight were compared with older and more overweight children, the OR rose to 4.55 (95% CI, 3.51-5.90) for obese children 16 to18 years of age. There was an apparent interaction between BMI and TCOL and BUN levels for the risk of hypertension. The risk for hypertension increased with higher TCOL level and lower GFR, but not with higher albumin level in obese children.

Discussion

The observed association between blood pressure and BMI is consistent with findings in other studies of general young population.[27-31] In a Spanish study, both SBP (112.6 ± 6.6 versus 107.8 ± 6.9 mm Hg) and DBP (65.9 ± 4.4 versus 64.2 ± 4.2 mm Hg) were higher in obese children than in non-obese children 6 to 16 years old.[27]

Sorof and Daniel concluded that obese children are at approximately 3-fold higher risk for hypertension than non-obese children.[5] In school children aged 10 to 19 years in Houston, overweight children were 3.26 times more likely than non-overweight children to have hypertension.[2] This study found that the estimated risk for hypertension in obese children was 3.45 times greater than that in children of normal weight. This excess risk might be partly attributable to the process of identification with abnormal urinary screening results. The dose-response relationship indicates an effect of BMI on childhood hypertension. Neter et al conducted a meta-analysis and indicated that blood pressure reductions were –1.05 mm Hg in SBP and –0.92 mm Hg in DBP per kilogram of body weight loss.[32]

Cholesterol elevation may also be associated with hypertension.[4,28] In students 5 to 18 years of age in the Netherlands, those with hypertension had higher TCOL than students without hypertension (4.3 ± 0.8 versus 3.9 ± 0.6 mmol/L, $P < .01$).[28] In this study, children with higher TCOL levels were more likely to have hypertension.

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Table II. Comparisons between case and control subjects by sex, age, body mass index, and selected physiological examinations with univariate and multivariate logistic regression

			Univariate	Multivariate
	Controls, % (n = 17 548)	Cases, % (n = 17 548)	OR (95% CI)	OR (95% CI)
Sex				
Girls	56.5	56.5	Reference	Reference
Boys	43.5	43.5	1.00 (–)	0.97 (0.93-1.02)
Age, years				
6-9	15.4	15.4	Reference	Reference
10-12	40.8	40.8	1.00 (–)	1.04 (0.97-1.11)
13-15	35.7	35.7	1.00 (–)	1.05 (0.98-1.13)
16-18	8.2	8.2	1.00 (–)	1.00 (0.91-1.10)
BMI status				
Normal weight	84.5	68.4	Reference	Reference
Overweight	9.5	13.7	1.79 (1.67-1.91)	1.77 (1.66-1.90)
Obesity	6.1	17.9	3.65 (3.39-3.93)	3.45 (3.20-3.72)
P for trend			<.0001	<.0001
TCOL, mg/dL				
<200	90.0	85.7	Reference	Reference
200-249	8.6	11.8	1.44 (1.34-1.54)	1.22 (1.14-1.32)
≥250	1.4	2.5	1.96 (1.67-2.30)	1.58 (1.34-1.87)
P for trend			<.0001	<.0001
Albumin, mg/dL				
<4.5	63.5	59.7	Reference	Reference
4.5-4.9	31.2	34.3	1.17 (1.12-1.23)	1.16 (1.10-1.21)
≥5.0	5.4	6.1	1.20 (1.09-1.31)	1.18 (1.07-1.30)
p for trend			<.0001	<.0001
BUN, mg/dL				
<23	99.1	98.9	Reference	Reference
≥23	0.9	1.1	1.22 (0.99-1.50)	1.12 (0.90-1.39)
GFR, mL/min/1.73m²				
≥60	83.4	81.5	Reference	Reference
<60	16.6	18.5	1.15 (1.09-1.21)	1.15 (1.02-1.31)

Missing data: 143 in BMI, 287 in TCOL, 286 in albumin, 278 in BUN, and 282 in CRE.

Consistent with other studies, this study also found BUN, CRE, or GFR and albumin may be associated with blood pressure elevation. Klag et al have demonstrated an association between blood pressure and BUN level in African-American subjects.[20] CRE level is an important marker of kidney function, which is also associated with hypertension and cardiovascular disease.[33-35] The ARIC study found a 2-fold increase in elevated CRE level associated with a 20 mm Hg increment in blood pressure in community residents.[36] The US Third National Health and Nutrition Examination Survey (NHANES) also showed that subjects with hypertension were 9 times more likely than subjects without hypertension to have elevated CRE levels.[34]

Increased serum albumin levels in adults are associated with elevated SBP ($P < .0001$), stroke, and coronary heart disease.[37] A Norwegian study of 5071 found that SBP increased 5 to 11 mm Hg in male subjects and 6 to 17 mm Hg in female subjects as the albumin levels increased from 4 to 5 g/dL.[38] This study observed that childhood blood pressure elevation is significantly associated with BUN, urinary CRE, and albumin levels, but this association is not as strong as in adults. This relationship was enhanced for obese children, more than 3 times greater.

The main limitation of this study is that all the study participants had positive urine screening results for proteinuria, hematuria, and/or glucosuria. The further screening program included no children with normal urine screening results in the check-up program for comparison. The risk estimation likely represents children with renal abnormalities and may not be generalized to the general population. The other limitation is that blood pressure was measured a single time. Therefore, we do not know if the subjects had hypertension, which would require persistence on repeat measurements or just elevated blood pressure on the date of the screening.

Table III. Hypertension risk in relation with body mass index in children with hematuria, proteinuria, and glucosuria

	Hematuria OR (95% CI) (n = 13 434)	Proteinuria OR (95% CI) (n = 20 912)	Glucosuria OR (95% CI) (n = 750)
BMI status			
Normal weight	Reference	Reference	Reference
Overweight	1.75 (1.58-1.94)	1.76 (1.60-1.93)	2.41 (1.35-4.29)
Obesity	3.21 (2.87-3.58)	3.64 (3.26-4.06)	3.98 (2.66-5.94)

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Table IV. Odds ratios and 95% confidence intervals for risk for hypertension associated with body mass index by sex, age, total cholesterol, blood urea nitrogen, and creatinine and albumin

	Status of body mass index		
	Normal weight aOR (95% CI)	Overweight aOR (95% CI)	Obesity aOR (95% CI)
Sex			
Girls	Reference	1.82 (1.66-1.98)	3.54 (3.20-3.92)
Boys	0.98 (0.93-1.03)	1.66 (1.49-1.84)	3.47 (3.11-3.87)
Age, years			
6-9	Reference	1.64 (1.40-1.93)	3.06 (2.57-3.65)
10-12	1.02 (0.95-1.10)	1.75 (1.56-1.96)	3.28 (2.89-3.72)
13-15	1.01 (0.93-1.09)	1.78 (1.56-2.04)	3.99 (3.46-4.60)
16-18	0.88 (0.79-0.98)	2.31 (1.78-3.01)	4.55 (3.51-5.90)
TCOL, mg/dL			
<200	Reference	1.75 (1.63-1.88)	3.42 (3.15-3.71)
200-249	1.21 (1.11-1.32)	2.16 (1.78-2.63)	5.17 (4.29-6.21)
≥250	1.54 (1.26-1.88)	4.02 (2.56-6.32)	6.15 (4.12-9.18)
Albumin, mg/dL			
<5.0	Reference	1.78 (1.66-1.90)	3.59 (3.33-3.88)
≥5.0	1.15 1.04-1.28	1.91 (1.46-2.50)	3.26 (2.45-4.35)
BUN, mg/dL			
<23	Reference	1.77 (1.65-1.89)	3.55 (3.29-3.83)
≥23	1.13 0.90-1.43	2.17 (1.05-4.48)	3.66 (1.74-7.73)
GFR, mL/min/1.73m²			
≥ 60	Reference	1.79 (1.67-1.92)	3.53 (3.27-3.81)
<60	1.18 (1.03-1.36)	1.47 (1.03-2.11)	5.14 (3.43-7.72)

Obesity was the most important factor associated with blood pressure elevation, followed by hyperlipidemia, elevated urea nitrogen, CRE, and albumin levels in this population with abnormal urinalysis results. Further studies are needed to investigate the health effect of childhood hypertension in this population. ■

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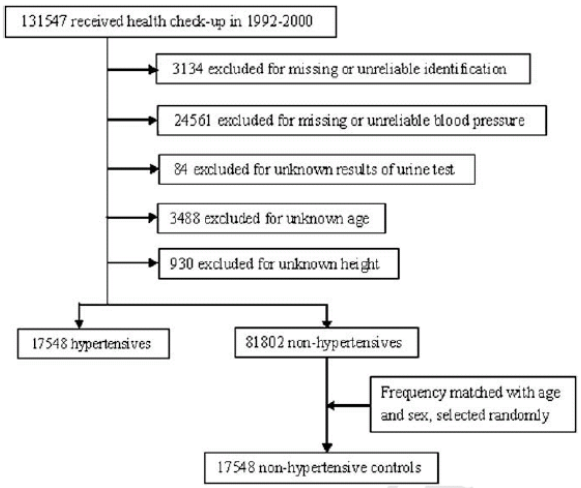

Figure. Procedures to select children with hypertension and control subjects.

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Table I. Comparisons between case and control subjects in blood pressure, cholesterol, serum albumin, blood urea nitrogen, and serum creatinine levels by body mass index

	Status of BMI			
	Normal weight, mean ± SD (n = 26 722)	Overweight mean ± SD (n = 4050)	Obesity (n = 4181)	*P* value for trend
SBP, mm Hg				
Cases	123.4 ± 11.5	125.6 ± 11.4	130.2 ± 13.5	<.0001
Controls	104.3 ± 11.3	106.6 ± 11.3	108.4 ± 11.0	<.0001
Difference	19.16	18.92	21.80	<.0001†
P *	<.0001	<.0001	<.0001	
DBP, mm Hg				
Cases	79.3 ± 9.3	79.1 ± 9.0	81.7 ± 10.4	<.0001
Controls	65.2 ± 8.7	66.3 ± 8.6	67.5 ± 8.4	<.0001
Difference	14.08	12.86	14.15	.5349†
P *	<.0001	<.0001	<.0001	
TCOL, mg/dL				
Cases	164.7 ± 39.1	168.4 ± 46.2	178.1 ± 46.0	<.0001
Controls	160.5 ± 34.6	163.0 ± 33.8	168.9 ± 37.8	<.0001
Difference	4.21	5.35	9.13	.0001†
P *	<.0001	.0052	<.0001	
Albumin, mg/dL				
Cases	4.40 ± 4.07	4.37 ± 1.21	4.35 ± 0.42	.4705
Controls	4.33 ± 0.67	4.33 ± 0.39	4.74 ± 13.2	.0009
Difference	0.07	0.04	−0.39	.0019†
P *	<.0001	.0877	.0436	
BUN, mg/dL				
Cases	12.36 ± 5.67	12.29 ± 5.68	12.57 ± 3.59	.1093
Controls	12.38 ± 11.6	12.28 ± 4.86	12.62 ± 4.15	.4705
Difference	−0.02	0.01	−0.06	.9093†
P *	.2377	.3088	.5410	
CRE, mg/dL				
Cases	1.06 ± 0.34	1.11 ± 2.25	1.08 ± 0.24	.1168
Controls	1.05 ± 0.24	1.04 ± 0.23	1.06 ± 0.35	.1930
Difference	0.01	0.06	0.02	.4192†
P *	.0553	.3351	.0016	
GFR				
Cases	90.2 ± 23.5	90.7 ± 20.0	90.3 ± 20.4	.5600
Controls	90.6 ± 20.4	90.0 ± 21.0	90.0 ± 21.1	.7709
Difference	−0.39	0.68	0.32	.9204†
P *	.0578	.2123	.6118	
HTN stage 1, %	38.7	49.6	52.2	<.0001
HTN stage 2, %	6.0	9.5	22.5	<.0001

HTN, Hypertension.
*Wilcoxon rank sum test between case and control subjects.
†Test for interaction between difference and BMI status.

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