PHYSICAL FITNESS AND CARDIOVASCULAR RISK FACTORS IN CHILDREN

AN EPIDEMIOLOGICAL PERSPECTIVE

Omslag

Frans de Man

Drukwerk

Offsetdrukkerij Haveka B.V., Alblasserdam

PHYSICAL FITNESS AND CARDIOVASCULAR RISK FACTORS IN CHILDREN

AN EPIDEMIOLOGICAL PERSPECTIVE

Lichamelijke conditie en risicofactoren voor hart- en vaatziekten bij kinderen

Een epidemiologisch gezichtspunt

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof.Dr. C.J. Rijnvos
en volgens besluit van het College van Dekanen.
De openbare verdediging zal plaatsvinden op
woensdag 29 mei 1991 om 15.45 uur.

door

Stijnie Arnolda de Man

geboren te Gouda

Promotie commissie:

Promotor:	Prof.Dr. A. Hofman
Co-promotor:	Dr. D.E. Grobbee
Overige leden:	Prof.Dr. J.C. Birkenhäger
	Prof.Dr. J. Hess
	Prof.Dr. W.L. Mosterd

Aan mijn ouders

Aan Paul

Acknowledgement

This study has generously been supported by the Netherlands Prevention Fund.
The Netherlands Heart Foundation, Mijnhardt B.V. te Bunnik, 3M Nederland B.V. te Zoeterwoude, Bristol Meyers Squibb te Woerden and the Rotterdam Medical Research Foundation are gratefully acknowledged for providing support to make the publication of this thesis possible.

Contents

Publications and manuscripts based on the studies described in this thesis

Chapter 2.2 Physical activity and the lipoprotein profile in the young. A review of recent studies (submitted).

Chapter 4.1 Diastolic blood pressure is inversely related to physical fitness in children (submitted).

Chapter 4.2 Blood pressure, physical fitness and hemodynamic characteristics in childhood (submitted).

Chapter 5. Physical fitness, serum lipids and lipoproteins in childhood.
Am J Epidemiol (in press).

Chapter 6.1 Effect of weight loss and exercise on blood pressure: a randomized trial in overweight children (submitted).

Chapter 6.2 Effect of exercise and weight reduction on plasma lipids and lipoproteins in overweight children (submitted).

Appendix Blood pressure in childhood: Pooled findings of six European studies.
J Hypertension 1991;9:109-14.

CHAPTER 1

INTRODUCTION

An agent with lipid-lowering, antihypertensive, positive inotropic, negative chronotropic, vasodilating, diuretic, anorexigenic, weight-reducing, cathartic, hypoglycemic, tranquilizing, hypnotic and antidepressive qualities (Am J Cardiol 1984;53:261).

1. INTRODUCTION

From the statement "Anyone who sits around idle and takes no exercise will be subject to physical discomfort and failing strength" made by the twelfth-century scholar and physician Rabbi Moses Maimonides in the Mishneh Torah, can be inferred that since ancient times physical activity has been viewed as a means of preserving and enhancing health and quality of life. In our industrialized society, deprived from natural stimuli to exercise, physical activity has increasingly been a subject of study, especially with regard to the leading cause of mortality, cardiovascular disease. One of the first observational studies on this subject was performed by Morris et al. who reported that physically active London conductors on double-decker buses and postmen had a lower incidence of cardiovascular events compared to sedentary bus drivers, postal clerks, and governmental civil servants (1). Blair et al. recently demonstrated that physical fitness appeared to be an important independent determinant of all-cause mortality in women and men, which was largely explained by reduced rates of cardiovascular disease and cancer deaths in the more-fit men and women (2). In order to further unravel the preserving and enhancing qualities of physical activity with regard to cardiovascular health, several studies reported an inverse relation between physical activity and cardiovascular risk factors, notably blood pressure (3) and serum lipids (4). These data suggest that exercise might both have an independent effect on the occurrence of cardiovascular disease and modify its risk factors.

Physical fitness can be viewed as an intermediate factor, responsible for the observed relations between physical activity and cardiovascular risk factors, although the possibility cannot be ruled out that improvement of cardiovascular health may be due to biologic consequences of increased activity different from those associated with the improvement in fitness (5).

Evidence accumulates, indicating that the development of an elevated blood pressure and of atherosclerosis are consequences of processes that start early in life (6,7). Also, intervention on blood pressure and the lipid profile at a young age remains largely restricted to non-pharmacologic means, i.e. diet and exercise. This provides a rationale to study physical fitness as a possible determinant of cardiovascular risk factors, both blood pressure and the lipid profile, in childhood. In this way, knowledge may be increased about the aetiology of these cardiovascular risk factors and indicate ways of prevention of cardiovascular damage at an early stage.

In chapter 2 studies on physical activity, physical fitness and cardiovascular risk factors in children and adolescents are reviewed. The design, populations and methods of the studies presented in this thesis are described in chapter 3. In chapter 4 the results of a large observational study in schoolchildren concerning the relation between physical fitness, blood pressure, and hemodynamic characteristics, are described. Physical fitness was studied also as a determinant of the lipoprotein profile in the same study population. This is presented in chapter 5. A randomized trial was conducted in order to assess the effect of exercise and weight reduction on blood pressure in overweight children. In the same study, effects on plasma lipids and lipoproteins were investigated. The results are described in chapter 6. Finally, chapter 7 will deal with general aspects of prevention of atherosclerosis in childhood, based on the conclusions derived from the described studies.

References

1. Morris JN, Heady JA, Raffle PAB, Roberts C, Parks J. Coronary heart disease and physical activity of work. Lancet 1953;ii:1053-7,1111-20.
2. Blair SN, Kohl HW, Paffenbarger RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all cause mortality: A prospective study of healthy men and women. JAMA 1989;262:2395-401.
3. Fagard R, M'Buyamba JR, Staessen J, Vanhees L, Amery A. Physical activity and blood pressure. In: Bulpitt CJ, ed. Handbook of Hypertension. Vol 6. Epidemiology of Hypertension. Amsterdam: Elsevier, 1985;104-30.
4. Haskell WL. Exercise-induced changes in plasma lipids and lipoproteins. Prev Med 1984;13:23-36.
5. Haskell WL. Physical activity and health: Need to define the required stimulus. Am J Cardiol 1985;55:4D-9D.
6. Hofman A. Blood pressure in childhood. Epidemiological probes into the aetiolology of high blood pressure. Thesis. Rotterdam, 1983.
7. Van Stiphout WAHJ. Serum lipids in the young. An epidemiological view of early atherogenesis. Thesis. Rotterdam, 1986.

CHAPTER 2

CARDIOVASCULAR RISK FACTORS AND PHYSICAL ACTIVITY

2.1 A REVIEW OF PHYSICAL ACTIVITY AND BLOOD PRESSURE IN YOUNGSTERS

Introduction

The relation between blood pressure and physical activity has been extensively studied in particular in male adults. Although conflicting results remain, in general an inverse relation has been reported at adult age (1).

Evidence is accumulating to suggest that there is a degree of stability of peer rank order of blood pressure during the first decades of life (2-7). This would suggest that adult hypertension may begin in childhood. Therefore, determinants of blood pressure during childhood may not only be important as predictors of adult blood pressure levels, but may as well provide ways for prevention of primary hypertension at a young age. The available reports from studies on physical activity, i.e. daily physical activity and physical fitness, as determinant of blood pressure early in life will be discussed with special emphasis on methodologic aspects in the following paragraphs. Daily physical activity is defined as the total amount of daily movements and physical fitness as physical performance capacity. The characteristics and findings from the observational studies are summarized in Table 2.1.1 and from the experimental studies in Table 2.1.2.

Observational studies

Daily physical activity

Findings from an Italian study in 272 children, aged 11 years, showed that daily physical activity during leisure time, assessed by questionnaire, was associated with higher systolic blood pressure. Although the authors reported a slight, non-significant, difference in body weight and adiposity between sedentary and active children, they did not take anthropometric variables into account as confounders of the relation between blood pressure and daily physical activity (8).

In three studies both daily physical activity and physical fitness were studied in relation to blood pressure (9-11). No association was reported between blood pressure and daily physical activity in 290 boys and girls, aged 12 years, by Sallis et al. (9). Three blood pressure readings were taken. Daily physical activity was assessed in two ways. First, from a seven-day physical activity recall questionnaire, total energy expenditure was derived and expressed in kilocalories per kg per day. Second, a five-point scale ranging from much less active to much more active was used for the question of how much physical activity was performed compared to others. No

Table 2.1.1. Characteristics and findings from observational studies on daily physical activity, physical fitness and blood pressure in children.

Reference	*Number*		*Age*	*Methods of blood*	*Methods of physical activity*	*Adjustments*	*Results*	
	Boys	*Girls*	*(yrs)*	*pressure assessment*	*assessment; units*	*anthropometry*	*SBP*	*DBP*
Daily physical activity								
Strazzulo (8)	153	119	11	mean two readings; random zero sphygmomanometer	questionnaire; categories of activity	-	↓	0
Sallis (9)	148	142	12	three readings; random zero sphygmomanometer	questionnaire sevenday recall; energy expenditure in kcal/kg/day	-	0	0
Tell (10)	413	372	13	mean two readings; random zero sphygmomanometer	questionnaire; frequency intensive exercise	+	0	0
Verschuur (11)	195	215	14	?	questionnaire, pedometer, heart rate recording	-	0	0
Physical fitness								
Gutin (12)	107	109	6	mean four readings; automatic device	submaximal treadmill test; PWC_{170}*	+	0	0
Hofman (13)	1,047	1,014	9	mean two readings; standard sphygmomanometer	modified Harvard step test; postexercise pulse rate	+	↓	↓
Hansen (14)	649	635	10	one reading; random zero sphygmomanometer	maximal cycle test; indirect VO_2max/kg**	+	0	0
Panico (15)	743	598	12	mean two readings; standard sphygmomanometer	modified Harvard step test; postexercise pulse rate	+	↓ (boys)	0

continued...

Table 2.1.1. (cont.)

Sallis (9)	148	142	12	three readings; random zero sphygmomanometer	submaximal cycle test until at 85% of maximal heart rate; indirect VO_2max/kg	+	↓ (boys)	0
Tell (10)	413	372	13	mean two readings; random zero sphygmomanometer	submaximal cycle test until heart rate at 140-160; indirect VO_2max/kg	+	↓	↓
Verschuur (11)	195	215	14	?	submaximal treadmill test; indirect VO_2max/kg	-	↓ (boys)	0
Fraser (16)	270		7-13	one reading; standard	submaximal treadmill test;	+	↓ (boys)	0
			13-17	sphygmomanometer	PWC_{170}	+	↓	0
Wilson (17)	34	68	14	three readings; random zero sphygmomanometer	maximal cycle test; VO_2max/kg	-	↓ (girls)	↓
Fripp (18)	37		15	?	maximal treadmill test; VO_2max/kg	+	0	0

* Physical work capacity at heart rate 170; ** Maximal oxygen uptake
Findings: 0=no relation; ↑=increase; ↓=decrease

adjustments were made for additional confounding as body mass index. Tell and Vellar (10) reported no relation between daily physical activity, as measured by a self-report question on frequency of intensive leisure time exercise, and blood pressure in 10-14 year old boys and girls. The mean of two blood pressure readings was used and adjustments were made for body mass index and sexual maturity rating. In 13 to 14 year old boys and girls no relation was reported by Verschuur et al. between daily physical activity and blood pressure (11). Daily physical activity was measured in three ways, by questionnaire regarding the past three months, by measuring the heart rate during 48 hours which was expressed as energy expenditure per kg body weight and energy expenditure per 24 hours, and by pedometers.

Physical fitness

Gutin et al. recently reported on blood pressure and physical fitness in 5 and 6 year children (12). The study population consisted of children from one parent householdings with a low-income. They were mainly recruted from one outpatient pediatric clinic. All data were mean values of two laboratory visits. Blood pressure was measured with an automatic device and the average of the last four of five measurements was obtained. Physical fitness was assessed during a submaximal treadmill test and expressed as the percent grade corresponding to a heart rate of 170. After adjustment for parental blood pressure and sum of skinfolds, no relation could be found between blood pressure and physical fitness. Hofman and co-workers studied blood pressure and physical fitness in a study population of 2,061 children, aged 9 years (13). The children participated in a multiple factor intervention study on cardiovascular risk factors for 1 year. The average blood pressure of the second and the third reading was used and physical fitness was assessed by a modified Harvard step test and expressed as postexercise sum of pulse rates. After 1 year no changes in physical fitness were observed. The authors subsequently adjusted for age, race, area of residence, resting pulse rate, ponderosity index and intervention status and analyzed the data as if obtained in an observational study. The authors reported that systolic and diastolic blood pressure were highest in children with a poor physical fitness. Hansen et al. showed in 1,284 children aged 10 years, after adjustment for age, heart rate, height, and body mass index, that no relation could be found between blood pressure and physical fitness (14). Blood pressure was measured once and physical fitness was expressed in ml/kgmin derived from a calculated index of maximal mechanical power and body weight. Panico and co-workers reported an inverse unadjusted association between systolic blood pressure and physical fitness in 1,341 children aged 7 to 14 years

(15). After confounding variables as age, body mass index, height and resting pulse rate were taken into account, only boys with a higher fitness had a lower systolic blood pressure. Blood pressure and physical fitness were measured similarly as in reference (13). An inverse association was reported by Sallis et al. for diastolic blood pressure and physical fitness after adjustment for body mass index in 12 year old boys (9). No relation was found for girls, nor for systolic blood pressure. Physical fitness was measured during a submaximal cycle ergometer test and predicted maximal oxygen consumption, expressed per kg body weight, was calculated based on the heart rate during the final workload. In a study by Tell et al., physical fitness was predicted from the heart rate measured during submaximal bicycle exercise and expressed as maximal oxygen uptake per kg body weight (10). In those youngsters, aged 10-14 years, with the lowest physical fitness higher blood pressure levels were found, even after adjustment for sexual maturity rating and body mass index. Verschuur et al. reported on physical fitness and blood pressure in 13 to 14 year old boys and girls. With regard to physical fitness, boys with the highest level of maximal oxygen uptake, measured directly during a submaximal protocol, had lower systolic blood pressure. Fraser et al. studied physical fitness in 7 to 17 year old children (16). The 300 subjects were recruited selectively from the highest and the lowest part of the blood pressure distribution. Whether this was based on systolic, diastolic or mean arterial pressure was not reported. Physical fitness was measured submaximally and expressed as working capacity per kg body weight at a heart rate of 170. Adjustments were made for height, skinfold thickness and age, but not for body weight. An inverse relation with systolic blood pressure in preadolescent boys, aged 7 to 13 years, and adolescent boys and girls, aged 13 to 17 years, was reported. No relation with diastolic blood pressure was seen. Wilson et al. studied physical fitness in 14 year old adolescents with elevated blood pressure in comparison to controls matched for age, race, sex, and ponderal index (17). Blood pressure was considered elevated if on three different occasions blood pressure was at or above the 95th percentile and controls had blood pressure at or below the 50th centile. Physical fitness was assessed during a maximal protocol on a bicycle and oxygen uptake was measured continuously. Girls with elevated blood pressure had lower maximal oxygen uptake, either expressed per kg body weight or per lean body mass. Fripp and co-workers reported no association between blood pressure and aerobic capacity after adjustments were made for body mass index in 37 male adolescents, aged 15 years (18). Aerobic capacity was expressed as maximal oxygen uptake per kg body weight. The authors replied that body mass index was the main determinant of blood pressure and that if aerobic conditioning was used to intervene on blood pressure, it should be designed to result in a reduction of body weight in order to obtain maximum benefits. Yet, the study population was selected on having a low-to-moderate physical fitness, and only one third of the eligible respondents of whom 65% had a family history of hypertension or heart disease agreed to participate.

One study reported on the relation between change in physical fitness and change in blood pressure after one year (13) and after five years of follow-up (19), respectively. The children were 9 years old at baseline. After one year of follow-up an inverse relation was observed for systolic blood pressure in boys and girls and diastolic blood pressure in girls after adjustments for age, race, area of residence, resing pulse rate, intervention status, ponderosity index at baseline and change in ponderosity index. After five years of follow-up an inverse relation between change in systolic blood pressure and change in physical fitness was found in the control group of the multiple intervention study (19). Adjustments were made for age, race, area of residence and ponderosity at baseline.

Experimental studies

Daily physical activity

Two studies reported on children participating in a multiple factor school-based intervention trial, the so-called "Know Your Body" program (20,21). Intervention consisted of advice on behaviour concerning nutrition, smoking and daily physical activity. Changes in daily physical activity, however, were not measured. After one year of intervention Walter et al. reported no change in physical fitness, expressed as a recovery index measured by Harvard step test in 9-10 year old children. Systolic blood pressure increased in the intervention group with 1.9 mmHg and in the control group with 4.1 mmHg. The net change in systolic blood pressure, adjusted for age, gender, race and baseline blood pressure, decreased with 1.9 mmHg in the intervention group. For diastolic blood pressure a net adjusted decrease of 1.8 mmHg was observed for the intervention group. Differences in changes of ponderosity index or triceps skinfold between the two study groups were not found. In North-Karelia 13 to 15 year old children participated in a similar intervention trial. After two years no effect on blood pressure was found. Daily physical activity or physical fitness were not measured.

Physical fitness

Jones and co-workers studied the effect on blood pressure after a 12-week aerobic exercise program, consisting of 30 minutes four times per week of exercise at an intensity of 70-85% of the predicted maximal heart rate in a randomized trial with 8

Table 2.1.2. Characteristics and findings from experimental studies on daily physical activity, physical fitness and blood pressure in children.

Reference	*Number*	*Age (yrs)*	*Population; control group*	*Intervention time; type*	*Methods of physical activity assessment; change in units*	*Change (mmHg)*	
						SBP	*DBP*
Daily physical activity							
Walter (20)	1,115	9	schoolchildren control +	one year; educational lessons in school	modified Harvard step test; postexercise pulse rate	- 2	- 2
Puska (21)	851	13	schoolchildren; control +	two years; educational lessons in school	-	0	0
Physical fitness							
Jones (22)	180	9	schoolchildren control -	12 weeks; 30 min 4 days per week at 80% maximal heart rate	submaximal cycle test; ?	+ 1.2	- 0.1
Dwyer (23)	216	10	schoolchildren control +	14 weeks; 75 min 5 days per week	submaximal cycle test; PWC_{170}/kg ↑*	0	0
Dwyer (23)	216	10	schoolchildren control -	2 years; 75 min 5 days per week	submaximal cycle test; PWC_{170}/kg ↑	0	- 7
Hagberg (24)	25	16	hypertensive students control -	6 months; 35 min 5 times per week at 75% VO_2max	maximal treadmill test; VO_2max/kg ↑**	- 8	- 5

* Physical work capacity at heart rate 170; ** Maximal oxygen uptake

and 9 year old children (22). He reported a slight increase in systolic blood pressure and no change in diastolic blood pressure. Effects on body weight parameters were not reported. Dwyer et al. reported that after an intervention of 14 weeks of 75 min of aerobic exercise during 5 days per week no change in blood pressure could be observed in comparison to the control group (23). From the same study a lower diastolic blood pressure compared to base-line was reported in 11 year old boys who participated for two years in the intervention program. Also, a significant reduction of body fat was found. Hagberg et al. found a decrease in systolic and diastolic blood pressure in hypertensive adolescents of 8 and 5 mmHg, respectively. They were aged 16 years and participated in a 6 months exercise program of five times per week 45 minutes at an intensity of 70-80% of the maximal oxygen uptake (24). Maximal oxygen capacity increased after the intervention and no change in body weight was observed. Unfortunately, the study did not comprise a control group.

Conclusion

When the results of the reported studies on daily physical activity in children are taken together, there is little evidence of a relation between daily physical activity and blood pressure. This absence of an association appears not to depend on the method used to assess daily physical activity.

In general, lower blood pressure levels are found in children with higher levels of physical fitness, mainly in boys. The observed association seems not to depend on age and method to assess physical fitness, but could be gender related.

Experimental results on multiple factor intervention trials, including daily physical activity, are difficult to interpret, as the effect of different types of intervention on the outcome parameter, blood pressure, cannot be separated. Nonetheless, a decrease in blood pressure was observed after one year of intervention. Also a decrease in blood pressure, mainly diastolic, is found after intervention on physical fitness, although lack of control groups hamper this conclusion.

References

1. Fagard R, M'Buyamba JR, Staessen J, Vanhees L, Amery A. Physical activity and blood pressure. In: Bulpitt CJ, ed. Handbook of Hypertension. Vol 6. Epidemiology of Hypertension. Amsterdam: Elsevier, 1985;104-30.
2. Clarke WR, Schrott H, Leaverton PE, Connor WE, Lauer RM. Tracking of blood lipids and blood pressure in children. Circulation 1978;58:626-34.

3. Voors W, Webber LS, Berenson GS. Time course studies of blood pressure in children. The Bogalusa Heart Study. Am J Epidemiol 1979;109:320-34.
4. Rosner B, Hennekens CH, Kass EH, Miall WE. Age-specific correlation analysis of longitudinal blood pressure data. Am J Epidemiol 1977;106:306-13.
5. Hiat HI, Lemeshow S, Rosenman KD. A longitudinal study of blood pressure in a national survey of children. Am J Pub Health 1982;172:1285-7.
6. Ware JH, Wu MC. Tracking: Prediction of future values from serial measurements. Biometrics 1981;37:427-37.
7. Hofman A, Valkenburg HA, Maas J, Groustra FN. The natural history of blood pressure in childhood. Int J Epidemiol 1985;14:91-6.
8. Strazzulo P, Cappuccio FP, Trevisan M, De Leo A, Krogh V, Giorgione N, Mancini M. Leisure time physical activity and blood pressure in schoolchildren. Am J Epidemiol 1988;127:726-33.
9. Sallis JF, Patterson TL, Buono MJ, Nader PR. Relation of cardiovascular fitness and physical activity to cardiovascular disease risk factors in children and adults. Am J Epidemiol 1988;127:933-41.
10. Tell GS, Vellar OD. Physical fitness, physical activity and cardiovascular disease risk factors in adolescents: The Oslo Youth study. Prev Med 1988;17:12-24.
11. Verschuur R, Kemper HCG, Besseling CWM. Habitual physical activity and health in 13- and 14-year-old teenagers. In: Ilmarinen J, Välimäki, eds. Children and Sport. Springer-Verlag: Berlin/Heidelberg, 1984;255-60.
12. Gutin B, Basch C, Shea S, Contento I, DeLozier M, Rips J, Irigoyen M, Zybert P. Blood pressure, fitness, and fatness in 5- and 6-year-old children. JAMA 1990;264:1123-27.
13. Hofman A, Walter HJ, Connelly PA, Vaughan RD. Blood pressure and physical fitness in children. Hypertension 1987;9:188-91.
14. Hansen HS, Hyldebrandt N. Blood pressure and physical fitness in a population of children, aged 8-10 years: The Odense school child study (abstract). 12th Scientific Meeting of the International Society of Hypertension, Kyoto, 1988.
15. Panico S, Celentano E, Krogh V, Jossa F, Farinaro E, Trevisan M, Mancini M. Physical activity and its relationship to blood pressure in school children. J Chron Dis 1987;40:925-30.
16. Fraser GE, Phillips RL, Harris R. Physical fitness and blood pressure in school children. Circulation 1983;67:405-12.
17. Wilson SL, Gaffney FA, Laird WP, Fixler DE. Body size, composition, and fitness in adolescents with elevated blood pressures. Hypertension 1985;7:417-22.
18. Fripp RR, Hodgson JL, Kwiterovich PO, Werner JC, Shuler HG, Whitman V. Aerobic capacity, obesity, and atherosclerotic risk factors in male adolescents. Pediatrics 1985;75:813-8.
19. Hofman A, Walter HJ. The association between physical fitness and cardiovascular disease risk factors in children in a five-year follow-up study. Int J Epidemiol 1989;18:830-5.
20. Walter HJ, Hofman A, Connelly PA, Barrett LT, Kost KL. Primary prevention of chronic disease in childhood: Changes in risk factors after one year ofintervention. Am J Epidemiol

1985;122:772-81.

21. Puska P, Vartiainen E, Pallonen U, Salonen JT, Pöyhiä P, Koskela K, McAlister A. The North Karelia Youth Project: Evaluation of two years of intervention on health behaviour and CVD risk factors among 13-15-year old children. Prev Med, 1982;11:550-70.
22. Jones T, Kozinetz C, Bermudez A, Mazur L, Kaplowitz H. Regular aerobic exercise and blood pressure in children: An efficacy school-based randomized clinical trial. Am J Epidemiol 1988;128:898-9.
23. Dwyer T, Coonan WE, Leithch DR, Hetzel BS, Baghurst RA. An investigation of the effects of dauly physical activity on the health of primary school students in South Australia. Int J Epidemiol 1983;12:308-13.
24. Hagberg JM, Goldring D, Ehsani AA, Heath GW, Hernandez A, Schechtman K, Holloszy JO. Effect of exercise training on the blood pressure and hemodynamic features of hypertensive adolescents. Am J Cardiol 1983;52:763-8.

2.2 PHYSICAL ACTIVITY AND THE LIPOPROTEIN PROFILE IN THE YOUNG: A REVIEW OF RECENT STUDIES

Introduction

In the Western world atherosclerotic cardiovascular disease (CVD) is one of the major contributors to chronic morbidity and mortality. Autopsy studies have indicated that atherosclerosis already begins in childhood (1-3). The mechanisms for development of early atherosclerotic lesions into CVD are not completely clear. However, serum lipid and lipoprotein levels are predictors of atherosclerotic lesions as well as CVD in adults (4). Insight in the etiology of CVD may be provided by studies on the determinants of lipids and lipoproteins in the young.

From the perspective of prevention, the potential effect of physical activity, i.e. physical fitness and daily physical acitvity, on the lipid and lipoprotein profile is of great importance. An increase in physical activity has shown to induce beneficial changes of the levels of serum lipids and lipoproteins in adults (5-8). In recent years the relation between physical activity and serum lipids in young people has been extensively investigated. This review describes recent results of studies in children and youngsters on the determinants of serum lipids and lipoproteins and their relation with physical activity.

Determinants of lipid and lipoprotein levels in children

Parent-offspring studies showed positive correlations for total cholesterol (TC) and high-density lipoprotein cholesterol (HDL) levels between parents and their children (9-11) and between siblings (11,12). When a family history of CVD existed, the offspring of these patients often had lower HDL (13-15) and lower apolipoprotein (apo) A-I levels (16). Comparisons of serum lipid and lipoprotein levels between races have indicated both similar TC levels in black and white children (17,18), and higher TC levels in black children (19-21). Triglycerides (TG) were higher in white children (18-22). HDL levels appeared higher in black children (18,20-22), although some studies did not report racial differences (23). The remaining lipoproteins showed no consistent differences between blacks and whites (21,22).

In most studies no relation between body weight and TC levels was found (24-26), while a negative relation was observed with HDL levels, mainly after puberty (10,24,26-28). The other lipids in general showed no relation with body weight (24, 26), although it was reported that TG and very low density lipoprotein cholesterol (VLDL) levels tended to increase with an increasing body weight (25).

Quetelet Index (QI) as an indicator of relative overweight as well as other measures of obesity showed significant positive relations with TC, TG, VLDL and low-density lipoprotein cholesterol (LDL) levels (20-22,26,29-32). QI showed either no relation with HDL (33-34), or tended to be negatively related to HDL (21,29). The relation between triceps skinfold and lipids followed a similar pattern (21,35-36,30).

Sexual maturation, expressed in Tanner stages, showed different lipid changes as compared to changes with chronological age, and therefore differences in CVD risk factor levels in childhood and adolescence may at least partly be due to differences in maturity and sex hormone levels (30,37-38). The use of oral contraceptives in girls tended to increase VLDL and LDL, and decrease HDL levels (20,30,39).

With regard to cigarette smoking, there seemed to be no relation with TC levels (20,21,26,39-41). Most studies reported a negative relation of smoking and HDL levels (20,21,26,40), while some studies found no such relation (10,41). Smoking had either no effect on VLDL, LDL and TG levels (21,26,39,41), or tended to elevate them (20,40).

Nutritional factors, like fat, cholesterol, carbohydrates, protein, and total energy intake appeared to have little correlations with lipids in youth (9,20,21,35,42). Calory-adjusted saturated fat intake tended to show a positive relation with TC (20, 42-43), and HDL levels (35,42). Alcohol appeared to have no consistent relation with lipids in youth (10,22,26).

In early life, lipids showed no clear relation with socio-economic status (18,23, 44). Inter-population studies had indicated higher levels of HDL in developed countries (44-46).

Daily physical activity and physical fitness

Measurement of daily physical activity intends to reflect the total amount of daily movements. Physical fitness is defined as physical performance capacity.

Quantification of daily physical activity in youth should reflect the normal amount of daily movements. Methods applied include estimates by parents, which are of doubtful validity (47-50); the use of diaries in children over 12 years of age (49,51), in which metabolic equivalent scores may be used as a measure of activity; the registration of heart rate during a certain time period (51); and movement counters like acto- and pedometers (51).

For measurement of physical fitness in youth, the treadmill is the ergometer of choice in children younger than 10 years of age (51-52). In older children, a cycle ergometer or a step test may be used. Physical fitness, usually defined as maximal aerobic capacity, is directly assessed in maximal test protocols, while in submaximal protocols, it is predicted from submaximal oxygen uptake and/or submaximal heart rate. The error involved in prediction, rather than direct assessment, is of less importance when groups are compared (51).

Non-experimental findings

Daily physical activity and the lipoprotein profile

Table 2.2.1 describes the populations and methods used in published studies on daily physical activity and lipids in youth (31,53-59). Most studies assessed daily physical activity by questionnaire, and compared high versus low active children. One study used metabolic equivalent scores (56), and another used heart rate recording and a pedometer (59) for daily physical activity assessment. Table 2.2.2 shows the results on associations between daily physical activity and lipids. Most studies found no significant assocation between daily physical activity and TC, while some observed a negative relation in children under 12 years of age (31,55). Daily physical activity on TG in children over 8 years old, showed either no, or a negative relation (56,58). With daily physical activity either no, or a positive association with HDL was observed in children of all ages (53-55,59), and with HDL/TC ratio in children over 8 years old (53,55-57). Gender differences in relations between daily physical activity and lipids were not consistent across the studies.

Physical fitness and the lipoprotein profile

Table 2.2.3 describes the populations and methods used in studies on physical fitness and lipids (24,34,47,54,57-66). In general, physical fitness was assessed by ergometer. Under 12 years of age, the most frequently used ergometer was the treadmill, while in older children treadmill and cycle ergometers were both frequently used. In most studies physical fitness was assessed in submaximal protocols and the findings were expressed in maximal oxygen consumption per kg body weight. As indicated in Table 2.2.4 no relation between physical fitness and TC was reported. Until puberty no association between physical fitness and TG was present. After puberty, TG levels showed either no relation, or decreasing levels were observed with increasing levels of physical fitness (24,58,61,63-65). Until puberty HDL levels showed no relation, while after puberty either no, or a positive relation was reported (24,58-59,61,63-65). LDL and VLDL levels were not associated with physical fitness. Two studies reported a possible relation between physical fitness and apolipoproteins in 16-18 year old children. For apo A a positive or no relation with physical fitness was observed and

Table 2.2.1. Characteristics of the published studies on lipids, lipoproteins and daily physical activity in children and youngsters.

Reference	*n*	*Sex*	*Age (yrs)*	*Methods of DPA* assessment*	*Study time*	*Data-analysis*
Viikari (53)	90	♂	3	questionnaire parent		
	94	♀		-calm/normal/busy child		
				-time spent outdoors		
Parizkova (54)	17	♂,♀	3-5	questionnaire teacher/parent	1 year	high v low active children
Wanne (55)	174	♂	8	questionnaire parent, child/teacher		no difference in weight in
				-grade physical education		high v low active children
				-regularity physical activity		
				-leisure time activity		
Thorland (56)	55	♂	8-11	questionnaire parent and child	5 days	no difference in weight in
				activity expressed in MET's**		high v low active children
Yamamoto (31)	1,763	♂,♀	7-12	schools with high and		age categories of
				low levels of exercise		7-9 and 10-12 years
Sallis (57)	290	♂,♀	10-12	questionnaire	7 days	
Viikari (53)	100	♂	12	questionnaire		
	100	♀		-leisure time activity		
				-grade physical education		
				-sport activity		
Tell (58)	413	♂	10-15	questionnaire		adjusted for sex and body mass
	372	♀		-regularity of intensive exercise		
Verschuur (59)	195	♂	13-14	questionnaire	3 months	high v low active children
	215	♀		pedometer	96 hours	
				heart rate recording	48 hours	

* Daily physical activity; ** Metabolic equivalent score

Table 2.2.2. Results from cross-sectional and longitudinal studies on lipids, lipoproteins and daily physical activity.

Ref	*n*	*Sex*	*Age (yrs*	*TC*	*TG*	*HDL*	*LDL*	*VLDL*	*HDL/TC*	*Comments*
53	184	♂,♀	3	0	0	0	0	0	-	
54	17	♂,♀	3-5	0	0	↑	0	-	-	
55	174	♂	8	↓	0	0	↓	-	↑	leisure time activity
				0	0	↑	0	-	↑	grade physical education
				↓	0	0	↓	-	0	regularity physical activity
56	55	♂	8-11	0	↓	0	-	-	↑	
31	1,763	♂,♀	7-12	↓	↓(ns)	↑(ns)	-	-	-	
57	148	♂	10-12	0	0	0	0	-	0	
	142	♀		0	0	0	0	-	↑	
53	100	♂	12	0	0	0	0	0	0	leisure time activity
				0	0	↑	0	0	↑	grade physical education
				0	0	0	0	0	↑	sport activity
	100	♀	12	0	0	0	0	0	0	leisure time activity
				0	0	0	0	0	↑	grade physical education
				0	0	↑	0	0	↑	sport activity
58	413	♂	10-15	0	0	0	-	-	0	
	372	♀		0	↓	0	-	-	0	
59	195	♂	13-14	0	-	0	-	-	-	
	215	♀		0	-	↑	-	-	-	

Findings: 0=no relation; ↑=increase; ↓=decrease; -=not studied; ns=not significant

Table 2.2.3. Characteristics of the studies on lipids, lipoproteins and physical fitness in children and youngsters.

Reference	*n*	*Sex*	*Age (yrs)*	*Methods of fitness assessment; units*	*Adjustments*	*Data-analysis*
Parizkova (54)	22	♂,♀	3-5	step test; heart rate		no weight, body fat difference in high v low active children
Saris (47)	171	♂,♀	4-6	submaximal treadmill test; PWC_{170}*		no weight, body fat difference in high v low active children
Saris (60)	800	♂,♀	6,8,10	submaximal treadmill test until heart rate at 170-180; indirect VO_2max/kg**		
Sady (34)	108	♂,♀	9-11	maximal treadmill test; VO_2max/kg	age, sex, fatness, TG	
Saris (47)	54	♂,♀	8-12	submaximal treadmill test; PWC_{170}		weight, body fat difference in high v low active children
Sallis (57)	148 142	♂ ♀	10-12	submaximal cycle test until at 85% of maximal heart rate; indirect VO_2max/kg	body mass index	
Välimäki (61)	31	♂,♀	11-13	maximal cycle test pulse conducted; PWC/kg		trained v untrained children
Tell (58)	413 372	♂ ♀	10-15	submaximal cycle test until heart rate at 140-160; indirect VO_2max/kg	sex, body mass index	
Montoye (62)	329	♂,♀	10-19	maximal treadmill test; VO_2max/kg	age, sex, weight, fatness	
Verschuur (59)	410	♂,♀	13-14	submaximal treadmill test; indirect VO_2max/kg		
Nizankowska (63)	73	♂,♀	14,5	-		no weight difference in exercise (45 min 10/wk) v control group (2/wk)
Wanne (24)	32 32	♂ ♀	14-16	maximal cycle test pulse conducted; PWC/kg		trained v untrained children
Fripp (64)	37	♂	15-17	treadmill test; VO_2max		

continued...

Table 2.2.3. (cont.)

Bell (65)	91	♂,♀	16-18	VO_2max	trained v untrained children
Rönnemaa (66)	25	♂	17	-	no difference in body mass index in endurance runners v controls

* Physical work capacity at heart rate 170; ** Maximal oxygen uptake

Table 2.2.4. Results from reported studies on lipids, lipoproteins and physical fitness in children and youngsters.

Ref	*n*	*Sex*	*Age (yrs)*	*TC*	*TG*	*HDL*	*LDL*	*VLDL*	*Apo A*	*Apo B*	*HDL/TC*
54	22	♂,♀	3-5	0	0	0	0	-	-	-	-
47	225	♂,♀	4-6	0	-	0	-	-	-	-	-
			8-12	0	-	0	-	-	-	-	-
60	800	♂,♀	6-10	0	-	0	-	-	-	-	↑
34	108	♂,♀	9-11	0	0	0	0	0	-	-	-
57	290	♂,♀	10-12	0	0	0	0	-	-	-	-
61	20	♂	11-13	0	0	↑	0	0	-	-	-
	11	♀		0	↓	0	0	0	-	-	-
58	413	♂	10-15	0	0	0	-	-	-	-	0
	372	♀		0	↓	↑	-	-	-	-	↑
62	329	♂,♀	10-19	0	0	-	-	-	-	-	-
59	195	♂	13-14	0	-	0	-	-	-	-	-
	215	♀		0	-	↑	-	-	-	-	-
63	73	♂,♀	14,5	0	↓	↑	0	-	-	-	-
24	32	♂	14-16	0	↓	↑	0	0	-	-	-
	32	♀		0	0	0	0	0	-	-	-
64	37	♂	15-17	0	↓	↑	0	-	-	-	-
65	91	♂,♀	16-18	0	↓	↑	↑	-	↑	↓	-
66	25	♂	17	↓(ns)	0	0	↓	-	0	↓	-

Findings: 0=no relation; ↑=increase; ↓=decrease; -=not studied; ns=not significant

apo B showed an inverse relation (65,66). An increase in HDL/TC ratio was observed with increasing levels of physical fitness (58,60).

Experimental findings

So far, experimental data concerning the effect of changes in daily physical activity or physical fitness are limited, in particular in young adults or children. The available data on the effects of daily physical activity and fitness intervention on serum lipids are summarized in Table 2.2.5 (15,50,67-74). A decrease in TC level may result from increases in daily physical activity intervention, combined with dietary advice (15,67-70). No effect of daily physical activity intervention on TG, HDL, LDL and VLDL levels could be observed. Physical fitness intervention studies showed increases in HDL, or HDL/TC ratio levels (67,72-74).

Table 2.2.5. Findings in intervention studies on daily physical activity, physical fitness and the lipoprotein profile in youngsters.

Reference	*n*	*Sex*	*Age (yr)*	*TC*	*TG*	*HDL*	*LDL*	*VLDL*	*HDL/TC*	*Comments*
Daily physical activity										
Szamosi (15)	77	♂,♀	2-18	↓	-	0	-	0	-	advice on DPA*, diet for 1 year; in FHC** children; with controls
Walter (67)	1,115	♂,♀	9	↓	-	0	-	-	↑	advice on DPA, diet, smoking for 1 year; with controls; adjusted for age, sex
Walter (68)	1,769	♂,♀	9	↓	-	0	-	-	-	advice on DPA, diet, smoking for 5 years
Widhalm (69)	14	♂	11-13	↓	↑(ns)	0	-	↑	-	daily sports program, 1000 cal/day diet for 3 weeks; obese subjects; with controls
Puska (9)	15	♂	13-15	↓	-	-	-	-	-	advice on DPA, diet, smoking for 2 years; with controls
	135	♀		↓	-	-	-	-	-	
Physical fitness										
Gilliam (71)	11	♂,♀	7-9	0	0	-	-	-	-	25 min 4 times per week moderate to heavy aerobic exercise for 12 weeks; with controls; 0 direct VO_2max/kg*** in cycle test
Gilliam (72)	14	♀	8-10	0	-	↑	-	-	↑	40 min 5 times per week strenuous exercise for 6 weeks; no controls
Dwyer (73)	175	♂,♀	10	0	0	0	-	-	-	75 min/day endurance exercise for 14 weeks; with controls; ↑ PWC_{170}/kg**** in cycle test

continued..

Table 2.2.5. (cont.)

Sasaki (74)	41	♂,♀	11	0	0	↑	-	-	-	20 min 7 times per week running exercise for 1 year in obese subjects; with controls; ↑ indirect VO_2max/kg
Linder (50)	50	♂	11-17	0	0	0	0	0	-	aerobic exercise for 8 weeks; with controls; ↑ PWC/kg in cycle test

* Daily physical activity; ** Family history of cardiovascular disease; *** Maximal oxygen uptake; **** Physical work capacity at heart rate 170
Findings: 0=none; ↑=increase; ↓=decrease; -=not studied; ns=not significant

Conclusion

Most studies on the relation lipids and daily physical activity report favorable associations. Higher levels of daily physical activity appear to be associated with higher levels of HDL and HDL/TC ratio. Relations between daily physical activity and lipids appear not to be gender related. A decrease in TC level may partly be due to changes with age (31). Relations of daily physical activity with TG and HDL levels are not explained by changes related to age. The observed associations appear not to depend on the method of assessment of daily physical activity. The physical education grade in school, of which some studies report a high correlation with lipids and other CVD risk factors compared to other methods of daily physical activity assessment (49,64), shows a consistent relation with HDL, and HDL/TC ratio (42,45).

Physical fitness appears to be favorably associated with TG, HDL, and apolipoprotein levels after puberty. In some studies relations between physical fitness and lipids are found in girls only (58,59,61), while others observe an association in boys (24,61,64,66). On balance, there seem to be no clear sex differences in relations between physical fitness and lipids. Changes in lipid levels with age do not account for the favorable associations between physical fitness and lipids. With the most accurate method for assessment of physical fitness, direct maximal oxygen consumption measurement, no relation between physical fitness and lipids is observed until puberty (34), while after puberty relations have been reported, using maximal as well as submaximal tests. Body weight is probably not very important as a confounder of physical fitness and lipids associations in the young, since body weight appears to be no determinant of serum lipids in this age group (10).

Combined intervention on daily physical activity and diet shows decreasing effects on TC. Although diet is not clearly a determinant of serum lipids in childhood, changes in diet may nonetheless be related to the lipoprotein profile.

Physical fitness intervention studies show an increase in HDL levels. Unfortunately, these studies are few. When an effect of physical fitness intervention on HDL level was reported, the intervention was long term (74), or intensive (72).

Only after puberty associations between physical fitness and lipids can be observed, in contrast to the associations of daily physical activity and lipids, which also are observed in young children. This difference may be due to the fact that physical fitness among young children is influenced by genetic characteristics rather than by daily physical activity (71,75,76). Klissouras (75), who studied physical fitness differences in identical twins, aged 7-13 years, could explain only 7% from differences in daily physical activity. However, Ilmarinen (77) showed in his study in adolescents that the amount of daily physical activity does indeed influence physical fitness.

In summary, a favorable relation between daily physical activity and lipids and lipoproteins in youth is documented most clearly for HDL and HDL/TC ratio. For physical fitness a favorable association with TG and HDL appears after puberty. However, more randomized controlled trials in children and youngsters are needed to study the intensity of physical activity required to reach a favorable lipid profile at a young age.

References

1. Newman WP, Freedman DS, Voors AW, Gard PD, Srinivasan SR, Cresanta JL, Williamson GD, Webber LS, Berenson GS. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. N Eng J Med 1986;314:138-44.
2. Tanaka K, Masuda J, Imamura T, Sueishi K, Nakashima T, Sakurai I, Shozawa T, Hosoda Y, Yoshida Y, Nishiyama Y, Yutani C, Hatano S. A nation-wide study of atherosclerosis in infants, children and young adults in Japan. Atherosclerosis 1988;72:143-56.
3. Berenson GS, Glueck CJ, Wissler RW, McGill HC. Summary and recommendations of the conference on blood lipids in children: Optimal levels for early prevention of coronary artery disease. Prev Med 1983;12:728-40.
4. Wallace RB, Anderson RA. Blood lipids, lipid-related measures, and the risk of atherosclerotic cardiovascular disease. Epidemiol Rev 1987;9:95-119.
5. Huttunen JK, Länsimies E, Voutilainen E, Ehmholm C, Hietanen E, Penttilä I, Siitonen O, Rauramaa R. Effect of moderate physical exercise on serum lipoproteins. A controlled clinical trial with special reference to serum high-density lipoproteins. Circulation 1979;60:1220-9.
6. Wood PD, Stefanick ML, Dreon DM, Frey-Hewitt B, Garay SC, Williams PT, Superko HR, Fortmann SP, Albers JL, Vranizan KM, Ellisworth NM, Terry RB, Haskell WL. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. N Engl J 1988;319:1173-9.
7. Hardman AE, Hudson A, Jones PRM, Norgan NG. Brisk walking and plasma high density lipoprotein cholesterol concentration in previously sedentary women. Br Med J 1989;299:1204-5.
8. Weintraub MS, Rosen Y, Otto R, Eisenberg S, Breslow JL. Physical exercise conditioning in the absence of weight loss reduces fasting and postprandial triglyceride-rich lipoprotein levels. Circulation 1989;79:1007-14.
9. Boulton TJC. Serum cholesterol in early childhood: Familial and nutritional influences and the emergence of tracking. Acta Paediatr Scand 1980;69:441-5.
10. Stiphout van WAHJ, Hofman A, Bruijn de AM, Valkenburg HA. Distributions and determinants of total and high-density lipoprotein cholesterol in Dutch children and young

adults. Prev Med 1985;14:169-80.

11. Morrison JA, Kelly K, Horvitz R, Khoury P, Laskarzweski PM, Mellies MJ, Glueck CJ. Parent-offspring and sibling lipid and lipoprotein associations during and after sharing of household environments: The Princeton school district family study. Metabolism 1982;31:158-66.
12. Morrison JA, Khoury P, Mellies MJ, Kelly KA, Glueck CJ. Identifying CHD risk factors in children: Intrafamilial lipoprotein correlations. Prev Med 1980;9:484-95.
13. Pometta D, Micheli H, Raymond L, Oberhaensli I, Suenram A. Decreased HDL cholesterol in prepubertal and pubertal children of CHD patients. Atherosclerosis 1980;36:101-9.
14. Moll PP, Sing CF, Weidman WH, Gordon H, Ellefson RD, Hodgson PA, Kottke BA. Total cholesterol and lipoproteins in school children: Prediction of coronary heart disease in adult relatives. Circulation 1983;67:127-34.
15. Szamosi T, Gara I, Venekei I, Jávor A, Ceskel R, Knoll J. Serum lipids, lipid peroxides and the care of children with high risk atherosclerotic family history. Atherosclerosis 1987;68:111-5.
16. Freedman DS, Srinivasan SR, Shear CL, Franklin FA, Webber LS, Berenson GS. The relation of apolipoproteins A-I and B in children to parental myocardial infarction. N Engl J Med 1986;315:721-6.
17. Wheeler RC, Marcus AC, Cullen JW, Konugres E. Baseline chronic disease risk factors in a racially heterogeneous elementary school population: The "Know your body" program, Los Angeles. Prev Med 1983;12:569-87.
18. Khoury PR, Morrison JA, Laskarzewski P, Kelly K, Mellies MJ, King P, Larsen R, Glueck CJ. Relationships of education and occupation to coronary heart disease risk factors in schoolchildren and adults: The Princeton school district study. Am J Epidemiol 1981;113:378-95.
19. Christensen B, Glueck C, Kwiterovich P, Degroot I, Chase G, Heiss G, Mowery R, Tamir I, Rifkind B. Plasma cholesterol and triglyceride distributions in 13,665 children and adolesents: The prevalence study of the Lipid Research Clinics Program. Pediatr Res 1980;14:194-202.
20. Berenson GS, Epstein FH. Conference on blood lipids in children: Optimal levels for early prevention of coronary artery disease. Prev Med 1983;12:741-97.
21. Khoury P, Morrison JA, Kelly K, Mellies M, Horvitz R, Glueck CJ. Clustering and interrelationships of coronary heart disease risk factors in schoolchildren, ages 6-19. Am J Epidemiol 1980; 112:524-38.
22. Freedman DS, Srinivasan SR, Webber LS, Burke GL, Berenson GS. Black-white differences in serum lipoproteins during sexual maturation: The Bogalusa Heart Study. J Chronic Dis 1987;40:309-18.
23. Williams CL, Carter BJ, Wynder EL. Prevalence of selected cardiovascular and cancer risk factors in a pediatric population: The "Know Your Body" project, New York. Prev Med 1981;10:235-50.
24. Wanne O, Viikari J, Välimäki I. Physical performance and serum lipids in 14-16-year-old trained, normally active, and inactive children. In: Ilmarinen J, Välimäki I, Eds. Children

and sport. Berlin: Springer-Verlag, 1984:241-6.
25. Laskarzewski P, Kelly KA, Mellies MJ, et al. Interrelationships of lipids, lipoproteins, and clinical chemistry measurements in 1605 schoolchildren, ages 6-17: The Princeton schoolchildren study. Metabolism 1980;29:916-23.
26. Glueck CJ, Heiss G, Morrison JA, Khoury P, Moore M. Alcoholintake, cigarette smoking and plasma lipids and lipoproteins in 12-19-year-old children. The collaborative lipid research clinics prevalence study. Circulation 1981;64 (suppl III):48-56.
27. Berenson GS, Srinivasan SR, Cresanta JL, Foster TA, Webber LS. Dynamic changes of serum lipoproteins in children during adolescence and sexual maturation. Am J Epidemiol 1981;113:157-70.
28. Beaglehole R, Trost DC, Tamir I, et al. Plasma high-density lipoprotein cholesterol in children and young adults. The lipid research clinics program prevalence study. Circulation 1980;62(suppl IV):83-92.
29. Laskarzewski P, Morrison JA, Mellies MJ, et al. Relationships of measurements of body mass to plasma lipoproteins in schoolchildren and adults. Am J Epidemiol 1980;111:395-406.
30. Berenson GS, Srinivasan SR, Frank GC, Webber MPH, Webber LS. Serum lipid and lipoprotein in infants and children and their relationship with diet. Nutr Child Health 1980:73-94.
31. Yamamoto A, Horibe H, Sawada S, et al. Serum lipid levels in elementary and junior high school children and their relationship to relative weight. Prev Med 1988;17:93-108.
32. Aristimuno GG, Foster TA, Voors AW, Srinivasan SR, Berenson GS. Influence of persistent obesity in children on cardiovascular risk factors: The Bogalusa Heart Study. Circulation 1984;69:895-904.
33. Lee J, Lauer RM, Clarke WR. Lipoproteins in the progeny of young men with coronary artery disease: Children with increased risk. Pediatrics 1986;78:330-7.
34. Sady SP, Berg K, Beal D, et al. Aerobic fitness and serum high-density lipoprotein cholesterol in young children. Hum Biol 1984;56:771-81.
35. Orchard TJ, Rodgers M, Hedley AJ, Mitchell JRA. Serum lipids in a teenage population: geografic, seasonal and familial factors. Int J Epidemiol 1981;10:161-70.
36. Freedman DS, Burke GL, Harsha DW, Srinivasan SR, Cresanta JL, Webber LS, Berenson GS. Relationship of changes in obesity to serum lipid and lipoprotein changes in childhood and adolescence. JAMA 1985;254:515-20.
37. Tell GS. Cardiovascular disease risk factors related to sexual maturation: The OsloYouth Study. J Chronic Dis 1985;38:633-42.
38. Laskarzewski PM, Morrison JA, Gutai J, Orchard T, Khoury PR, Glueck CJ. High and low density lipoprotein cholesterols in adolescent boys: relationships with endogenous testosterone, estradiol, and Quetelet index. Metabolism 1983;32:262-71.
39. Voors AW, Srinivasan SR, MacD Hunter S, Webber LS, Sklov MC, Berenson GS. Smoking, oral contraceptives, and serum lipid and lipoprotein levels in youths. Prev Med 1982;11:1-12.
40. Freedman DS, Srinivasan SR, Shear CL, Hunter SM, Croft JB, Webber LS, Berenson GS.

Cigarette smoking initiation and longitudinal changes in serum lipids and lipoproteins in early adulthood: The Bogalusa Heart Study. Am J Epidemiol 1986;124:207-19.

41. Freedman DS, Shear CL, Srinivasan SR, Webber LS, Berenson GS. Tracking of serum lipids and lipoproteins in children over an 8-year period: The Bogalusa Heart Study. Prev Med 1985;14:203-16.
42. Åkerblom HK, Viikari J, Uhari M, et al. A study of cardiovascular risk factors and their determinants in Finnish children. Ann Clin Res 1984;16:23-33.
43. Viikari J, Åkerblom HK, Seppanen A, Marniemi J, Sarna S. Atherosclerosis precursors in Finnish children and adolescents. Serum lipids, tracking of serum lipids, and preliminary results from cluster analyses of risk factors. Prog Clin Biol Res 1988;255:81-7.
44. Mendoza S, Contreras G, Ineichen E, et al. Lipids and lipoproteins in Venezuelan and American schoolchildren: Within and cross-cultural comparisons. Atherosclerosis 1980;14:272-7.
45. Knuiman JT, Hermus RJJ, Hautvast JGAJ. Serum total and high density lipoprotein (HDL) cholesterol concentrations in a rural and urban boys from 16 countries. Atherosclerosis 1980;36:529-37.
46. Halfon ST, Friedlander Y, Halperin G, et al. Plasma high-density lipoprotein cholesterol, total cholesterol and triglyceride levels in 17-year-old Jewish residents of Jerusalem: A preliminary report. The lipid research clinics program prevalence study. Circulation 1980;62 suppl IV:93-8.
47. Saris WHM, Binkhorst RA, Cramwinckel AB, Waesberghe van F, Veen-Hezemans van der AM. The relationship between working performance, daily physical activity, fatness, blood lipids, and nutrition in schoolchildren. In: Berg K, Eriksson BO, Eds. Children and exercise IX. Baltimore: University Park Press, 1980:166-74.
48. Murphy JK, Alpert BS, Christman JV, Willey JS. Physical fitness in children: A survey method based on parental report. Am J Public Health 1988;78:708-10.
49. Telama R, Viikari J, Valimaki I, et al. Atherosclerosis precursors in Finnish children and adolescents. X. Leisure-time physical activity. Acta Paediatr Scand 1985;318 suppl:169-80.
50. Linder CW, DuRant RH, Mahoney OM. The effect of physical conditioning on serum lipids and lipoproteins in white male adolescents. Med Sci Sports Exerc 1983;15:232-6.
51. Saris WHM. The assessment and evaluation of daily physical activity in children. A review. Acta Paediatr Scand 1985; suppl 318:37-48.
52. Bar-Or O. Procedures for exercise testing in children. In: Katz M, Stiehm ER, eds. Pediatric sports medicine for the practitioner. New York: Springer-Verlag, 1983:315-41.
53. Viikari J, Välimäki I, Telama R, et al. Atherosclerosis precursors in Finnish children: physical activity and plasma lipids in 3- and 12-year-old children. In: Ilmarinen J, Välimäki I, Eds. Children and sport. Berlin: Springer-Verlag, 1984:231-40.
54. Parizkova J, Mackova E, Kabele J, Mackova J, Skopkova M. Body composition, food intake, cardiorespiratory fitness, blood lipids and physiological development in highly active and inactive preschool children. Hum Biol 1986;58:261-73.
55. Wanne O, Viikari J, Telama R, et al. Physical activity and serum lipids in 8-year-old Finnish school boys. Scand J Sports Sci 1983;5:10-4.

56. Thorland WG, Gilliam TB. Comparison of serum lipids between habitually high and low active pre-adolescent males. Med Sci Sports Exercise 1981;13:316-21.
57. Sallis JF, Patterson TL, Buono MJ, Nader PR. Relation of cardiovascular fitness and physical activity to cardiovascular disease risk factors in children and adults. Am J Epidemiol 1988;127:933-41.
58. Tell GS, Vellar OD. Physical fitness, physical activity, and cardiovascular disease risk factors in adolescents: The Oslo youth study. Prev Med 1988;17:12-24.
59. Verschuur R, Kemper HCG, Besseling CWM. Habitual physicai activity and health in 13- and 14-year-old teenagers. In: Ilmarinen J, Välimäki I, Eds. Children and Sport. Berlin: Springer-Verlag, 1984:255-61.
60. Saris WHM, Noordeloos AM, Cramwinckel AB, Boeyen I, Elvers JWH, Veen van M, Köning KG, Binkhorst RA. Aerobic power, daily physical activity and some cardio-vascular disease risk indicators in children ages 6-10 years. In: WHM Saris. Aerobic power and daily physical activity in children: with special reference to methods and cardiovascular risk indicators. Meppel: Krips repro, 1982;153-76.
61. Välimäki I, Hursti M-L, Pihlakoski L, Viikari J. Exercise performance and serum lipids in relation to physical activity in schoolchildren. Int J Sports Medicine 1980;1:132-6.
62. Montoye HJ, Block WD, Gayle R. Maximal oxygen uptake and blood lipids. J Chron Dis 1978;31:111-8.
63. Nizankowska-Blaz T, Abramowicz T. Effects of intensive physical training on serum lipids and lipoproteins. Acta Paediatr Scand 1983;72:357-79.
64. Fripp RR, Hodgson JL, Kwiterovich PO, Werner JC, Schuler HG, Whitman V. Aerobic capacity, obesity, and atherosclerotic risk factors in male adolescents. Pediatrics 1985;75:813-8.
65. Bell RR, Macek M, Rutenfranz J. Blood lipoprotein profiles in trained and untrained adolescents. In: Oseid S, Carlsen K-H, Eds. Children and exercise XIII. Champaign: Human Kinetics, 1989:277-83.
66. Rönnemaa T, Lehtonen A, Jarvelainen H, Viikari J. Plasma lipids and lipoproteins of young male athletes and the effect of their serum on cultured human aortic smooth muscle cells. Scand J Sports Sci 1980;2:33-8.
67. Walter HJ, Hofman A, Connelly PA, Barrett LT, Kost KL. Primary prevention of chronic disease in childhood: changes in risk factors after one year of intervention. Am J Epidemiol 1985;122:772-81.
68. Walter HJ, Hofman A, Vaughan RD, Wynder EL. Modification of risk factors for coronary heart disease. Five-year results of a school-based intervention trial. N Eng J Med 1988;318:1093-100.
69. Widhalm K, Maxa E, Zyman H. Effect of diet and exercise upon the cholesterol and triglyceride content of plasma lipoproteins in overweight children. Eur J Pediatr 1978;127:121-6.
70. Puska P, Vartiainen E, Pallonen U, et al. The North Karelia Youth Project: Evaluation of two years of intervention on health behavior and CVD risk factors among 13- to 15-year old children. Prev Med 1982;11:550-70.

71. Gilliam TB, Freedson PS. Effects of a 12-week school physical fitness program on peak VO_2, body composition and blood lipids in 7 to 9 year old children. Int J Sports Medicine 1980;1:73-8.
72. Gilliam TB, Burke MB. Effects of exercise on serum lipids and lipoproteins in girls, ages 8 to 10 years. Artery 1978;4:203-13.
73. Dwyer T, Coonan WE, Leitch DR, Hetzel BS, Baghurst RA. An investigation of the effects of daily physical activity on the health of primary school students in South Australia. Int J Epidemiol 1983;12:308-13.
74. Sasaki J, Shindo M, Tanaka H, Ando M, Arakawa K. A long-term aerobic exercise program decreases the obesity index and increases the high density lipoprotein cholesterol concentration in obese children. Int J Obes 1987;11:339-45.
75. Klissouras V. Heritability of adaptive variation. J Appl Physiol 1971;31:338-44.
76. Åstrand PO. Experimental studies of physical working capacity in relation to sex and age. Copenhagen: Munksgaard, 1952.
77. Ilmarinen J, Rutenfranz J. Longitudinal studies of the changes in habitual physical acitvity of schoolchildren and working adolescents. In Children and Exercise X. Int Series on Sportsciences, 1981.

CHAPTER 3

STUDY DESIGN, POPULATIONS AND METHODS

3. STUDY DESIGN, POPULATIONS AND METHODS

Study design

The objective of the studies described in this thesis was to address determinants of cardiovascular risk at a young age. The main research questions were (1) is physical fitness associated with the cardiovascular risk factors blood pressure, serum lipids and lipoproteins in children and (2) can changes in physical fitness result in a change in blood pressure and the lipid profile in childhood.

Three studies of different design have been carried out: two non-experimental studies, a cross-sectional and a follow-up study, and an experimental study. In the cross-sectional part of the study the relation between levels of blood pressure, serum lipids, serum lipoproteins and levels of physical fitness was studied in a large population of schoolchildren. The follow-up study was carried out to investigate the relation between changes in physical fitness and changes in cardiovascular risk factors at a young age. Finally, the effect of exercise and body weight reduction on both blood pressure and plasma lipids and lipoproteins was studied in children with a relative overweight.

Study populations

Non-experimental studies

In 1987 a population of 1,774 schoolchildren, aged 7-11 years and residents of the town of Zoetermeer, the Netherlands, were invited for participation. These children were all 3th and 4th graders of a random sample of 28 schools out of 44 primary schools in Zoetermeer, a town of about 86,500 inhabitants at the time of this study. Data were collected during a time period of March 1987 to June 1988 at two examinations, a first one at the schools and a second one at a research center. At the first examination 1,613 children agreed to participate in the study (91%). One week after the school examination 1,558 children (757 boys) visited the research center for a second examination resulting in a response rate at the combined two examinations of 88%.

From February 1989 to July 1989 the follow-up study was carried out. Of the 1,558 children, who participated in the first part of the study, a random sample of 450 children was selected to participate in this longitudinal study. In addition, a sample of 216 children, who were relatively overweight during the first part of the study, was added to the study population. Relative overweight refers to the 25 percent of children who had the highest weight adjusted for differences in age and height, i.e. who were in the upper quartile of the age and height adjusted body weight distribution. Because 17 children had moved out of Zoetermeer, 649 children were invited for participation and 60 children refused to participate, resulting in a study population of 589 children (response rate 91%).

Experimental study

From the population of 589 children, who participated in the follow-up study on cardiovascular risk factors and physical fitness in childhood, 174 children were selected for the intervention study. Selection was based on the presence of a relatively high body weight, defined as a weight above the 75th centile of the age and height adjusted weight distribution at both examinations in the cross-sectional and follow-up study. 58 girls and 47 boys agreed to take part (response rate 60,3%) in a randomized controlled trial. They were randomly assigned to 3 study groups after being stratified according to sex and body weight adjusted for differences in chronological age and height.

Methods

Central in the described studies, apart from blood pressure and serum lipids, are measurements of physical fitness. Because the quality of the measurement instruments chosen are essential for the interpretation of the results, the applied method and its rationale will be described.

Physical fitness is usually determined submaximally and indirectly. In this study aerobic capacity was measured directly and with a maximal protocol. There is general agreement that the best method for maximal exercise testing in children below 10 years is a treadmill test (1). The Bruce test was chosen, because in this workload protocol the speed is variable so that even young children may perform the test without difficulty. In addition, reproducibility among children is high (2). Generally accepted criteria for reaching maximal exercise levels were used (3).

Physical fitness, defined as maximal aerobic capacity, was determined directly during a Bruce treadmill test by measuring maximal oxygen uptake (VO_2max) (4). According to this protocol, the speed as well as the gradient are increased every 3 minutes. The maximal exercise test on the treadmill was performed during the day in a room at a temperature between 18 and 22°C. The collected expired air volume was measured with a dry gas meter. Gas analyses were made continuously by a paramagnetic O_2 and an infrared CO_2 analyzer. Heart rate was calculated from a continuous ECG recording. Primary criteria for reaching maximal exercise were leveling off of oxygen uptake (i.e., no increase or less than 2 ml/kgmin) and/or leveling off of the heart rate despite an increased workload. Secondary criteria were a maximal respiratory gas exchange ratio greater than 1.0 and a maximal heart rate higher than the mean maximal heart rate minus two times the standard deviation, as given by Åstrand for the corresponding age (5).

References

1. WHO. Excercise tests in relation to cardiovascular function. Geneva: Technical Report Series; 1968;338.
2. Cumming GR, Everatt D, Hastman L. Bruce treadmill test in children: normal values in a clinic population. Am J Cardiol 1978;41:69-75.
3. Bar-Or O. Procedures for exercise testing in children. In: Katz M, Stiehm ER, eds. Pediatric sports medicine for the practitioner. New York: Springer-Verlag, 1983:305-41.
4. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973;85:546-62.
5. Åstrand PO. Experimental studies of physical working capacity in relation to sex and age. Copenhagen: Munksgaard, 1952.

CHAPTER 4

PHYSICAL FITNESS AND HEMODYNAMICS

4.1 DIASTOLIC BLOOD PRESSURE IS INVERSELY RELATED TO PHYSICAL FITNESS IN CHILDREN

Introduction

The causes of a raised arterial pressure are largely unknown, but the importance of hypertension as a risk factor for cardiovascular morbidity and mortality has been firmly established (1-3). There are studies suggesting that there is tracking of blood pressure from childhood to adult life, which implies that children with a blood pressure relatively high in comparison to other children of the same age and gender, tend to retain that ranking into adulthood (4-6). Therefore, determinants of blood pressure in childhood may be important in relation to blood pressure levels in adulthood.

Several studies reported an inverse association between physical fitness and blood pressure in adults (7,8,11) and showed a blood pressure decreasing effect of exercise intervention (9,10). Also, in youngsters (11-15) an inverse relation between blood pressure and physical fitness could be observed. In other studies, however, no association between physical fitness and blood pressure at a young age was found (16,17). Debate on this issue remains, in particular because the measurement of physical fitness is not well standardized. Also, variables as age and body weight, which may affect the relation between blood pressure and physical fitness and can easily be determined, have been taken into account in only a few studies.

This study was initiated to determine whether early in life physical fitness and blood pressure are related. Blood pressure and physical fitness were measured in a population of 1,558 Dutch schoolchildren, aged 7-11 years.

Methods

Population

A population of 1,774 schoolchildren, aged 7-11 years, was invited for participation in a study on physical fitness and cardiovascular disease risk indicators. These children were all third and fourth graders of a random sample of 28 schools out of 44 primary schools in Zoetermeer, a town of about 86,500 inhabitants in the Netherlands. During two examinations the data were collected. Firstly at the schools where 1,613 children (91%) were measured and secondly one week later 757 boys and 801 girls participated (88%) in the examination at the research center.

Measurements

During the study period from March 1987 until June 1988 the following variables were measured: height, body weight, sum of four skinfolds, blood pressure, pulse rate at rest, skeletal age, maximal oxygen consumption, maximal heart rate, and respiratory quotient.

Height and body weight were measured at the school examination with the children wearing no shoes and indoor clothes. Thickness of four skinfolds (biceps, triceps, subscapular, supra-iliac) was measured by a Holtain caliper (18).

Blood pressure was measured using a random-zero sphygmomanometer, with the child in sitting position on the left arm (19). Cuffs comfortably encircling the arm, usually a 23 x 10 cm^2 cuff, were used. Two measurements were taken, separated by a count of the pulse rate. The fifth Korotkoff phase was used as a measure of diastolic blood pressure. One week after the first phase the children visited the research center for a second examination. At this examination additional measurements, including physical fitness, were performed and blood pressure was remeasured by the same observer in the same way. In the analysis the average of the two blood pressure readings from the second examination was used.

Skeletal age was determined by a radiograph of the left hand. The radius, ulna and short finger bones were used to assign maturity scores and these were converted to skeletal age values according to Tanner et al. (20). All radiographs were read by one trained paramedical observer. Skeletal age was not measured in 93 children (55 girls) because the parents did not allow to make a radiograph of the hand, or because the children moved their hand during the recording.

Physical fitness, defined as maximal aerobic capacity, was determined directly during a Bruce treadmill test by measuring maximal oxygen uptake (VO_2max) (21). According to this protocol, the speed as well as the gradient are increased every 3 minutes. The maximal exercise test on the treadmill was performed during the day in a room at a temperature between 18 and 22°C. The collected expired air volume was measured with a dry gas meter. Gas analyses were made continuously by a paramagnetic O_2 and an infrared CO_2 analyzer. Heart rate was calculated from a continuous ECG recording. Primary criteria for reaching maximal exercise were leveling off of oxygen uptake (i.e., no increase or less than 2 ml/kgmin) and/or leveling off of the heart rate despite an increased workload. Secondary criteria were a maximal respiratory gas exchange ratio greater than 1.0 and a maximal heart rate higher than the mean maximal heart rate minus two times the standard deviation, as given by Åstrand for the corresponding age (22). The parents completed a questionnaire on the medical history of their children as part of the first examination. Based on this information 85 children were excluded from the exercise test for the following reasons:

asthma and chronic bronchitis (73), congenital heart disease (4), epilepsy (2), lung dysplasia (1), choanal atresia (1), diseases of the muscular and skeletal system (4). In 4 children multiple supraventricular extrasystoles appeared during exercise and consequently the test had to be stopped. A total of 149 children (10%) did not meet the criteria for reaching maximal exercise (71) or they did not follow the protocol correctly (78). Their data have not been used in the analysis. Consequently, complete data on physical fitness were available for 1,320 children. Mean values of age, anthropometric variables and blood pressure were similar in the children who were excluded from the analysis and those who did reach maximal aerobic capacity.

Data-analysis

Firstly, Pearson correlation coefficients of blood pressure and physical fitness with age, skeletal age, anthropometric characteristics, blood pressure, pulse rate and physical fitness were determined.

Secondly, a gender-specific linear regression model was used with blood pressure level as the dependent variable. Physical fitness, as independent variable, was expressed in absolute terms (VO_2max) and adjustments were made for differences in age, skeletal age, body weight, height and sum of four skinfolds.

Finally, blood pressure values were compared by quartiles of physical fitness, expressed in liters of maximal oxygen uptake per minute, for boys and girls separately. Cut-off points were 1.29, 1.44 and 1.61 liter/min of maximal oxygen uptake for boys, and 1.16, 1.29 and 1.42 liter/min for girls. Adjustments were made for differences in age, skeletal age, height, body weight and sum of four skinfolds.

Results

In Table 4.1.1 anthropometric characteristics, blood pressure, pulse rate at rest and findings on physical fitness are shown for boys and girls, separately. The sum of 4 skinfolds was higher in girls. Boys showed a higher mean maximal aerobic capacity, either in l/min or expressed per kg body weight.

Table 4.1.2 presents correlation coefficients of blood pressure and physical fitness with age, skeletal age, anthropometric variables, blood pressure, pulse rate and physical fitness. Both blood pressure and physical fitness showed strong correlations with anthropometric characteristics. Blood pressure appeared to be positively related to physical fitness. Physical fitness per kg body weight showed an inverse association with blood pressure in boys and girls.

Table 4.1.3 shows linear regression coefficients of blood pressure on physical

Table 4.1.1. Age, skeletal age, anthropometric characteristics, blood pressure, pulse rate, physical fitness, maximal heart rate and respiratory quotient for boys and girls separately.

	Boys		*Girls*	
Number	630		689	
Age (yrs)	8.4	(0.7)*	8.4	(0.7)
Skeletal age (yrs)	7.9	(1.4)	8.4	(1.3)
Height (cm)	134	(7)	134	(7)
Weight (kg)	29	(4)	29	(5)
Sum of 4 skinfolds (mm)	26	(11)	33	(13)
Systolic blood pressure (mmHg)	101	(9)	103	(9)
Diastolic blood pressure (mmHg)	58	(8)	60	(8)
Pulse rate (beats/min)	86	(12)	88	(12)
VO_2max (l/min)	1.46	(0.24)	1.30	(0.21)
VO_2max (ml/kgmin)	51.0	(6.2)	45.5	(5.5)
Maximal heart rate (beats/min)	205	(8)	208	(9)
Respiratory quotient	1.14	(0.10)	1.17	(0.10)

* Values are means with standard deviation in parentheses

fitness, both adjusted for age alone and for differences in age, skeletal age, body weight, height and sum of four skinfolds. After adjustment for differences in body size parameters, regression coefficients of systolic blood pressure on physical fitness changed from a positive association to no association. Diastolic blood pressure appeared to be inversely related to maximal aerobic capacity after adjustment for the various potential confounders in both boys and girls.

Figures 4.1.1 and 4.1.2 present mean blood pressure values by quartile of physical fitness, adjusted for differences in age, skeletal age, height, body weight and sum of four skinfolds. Category I corresponds to a relatively poor level of physical fitness and category IV to a relatively high level. For boys no difference in systolic blood pressure could be observed across the quartiles of maximal aerobic capacity. Systolic blood pressure in girls was lower in the first quartile of physical fitness, whereas no differences were present across the other three quartiles. Boys showed gradually lower levels of diastolic blood pressure from quartile I to IV of maximal aerobic capacity. For girls, diastolic blood pressure level was lowest in the fourth quartile of physical fitness.

Table 4.1.2. Correlation coefficients of systolic (SBP) and diastolic (DBP) blood pressure and physical fitness with age, skeletal age, anthropometric characteristics, blood pressure, pulse rate and physical fitness (VO_2max).

	Boys			*Girls*		
	SBP	*DBP*	*VO_2 max*	*SBP*	*DBP*	*VO_2 max*
Age	0.14	0.21	0.56	0.19	0.22	0.49
Skeletal age	0.15	0.15	0.50	0.28	0.22	0.46
Height	0.23	0.27	0.69	0.30	0.27	0.70
Body weight	0.30	0.33	0.67	0.39	0.37	0.70
Sum of skinfolds	0.23	0.20	0.14	0.27	0.25	0.27
SBP	-	0.44	0.21	-	0.42	0.32
DBP	0.44	-	0.17	0.42	-	0.20
Pulse rate	0.27	0.17	-0.14	0.23	0.11	-0.08
VO_2max	0.21	0.17	-	0.32	0.20	-
VO_2max/kg	-0.07^{ns}	-0.17	0.47	-0.10	-0.23	0.37

^{ns} All correlation coefficients are statistically significant at $p < 0.05$, except for one coefficient marked 'ns'

Table 4.1.3. Coefficients of linear regression with 95% confidence limits (between brackets) of systolic and diastolic blood pressure on physical fitness, defined as maximal oxygen uptake in l/min for boys and girls.

	Crude coefficient (mmHg/(l/min))*	*Adjusted coefficient** (mmHg/(l/min))*
Boys		
Systolic blood pressure	6.8 [3.5, 10.2]	2.1 [- 2.3, 6.5]
Diastolic blood pressure	3.0 [0.0, 6.5]	-5.8 [-10.0, -1.6]
Girls		
Systolic blood pressure	13.1 [9.4, 16.6]	4.4 [- 0.6, 9.4]
Diastolic blood pressure	4.4 [1.2, 7.5]	-7.3 [-11.6, -3.0]

* Adjusted for age; ** Adjusted for age, skeletal age, height, body weight, sum of skinfolds

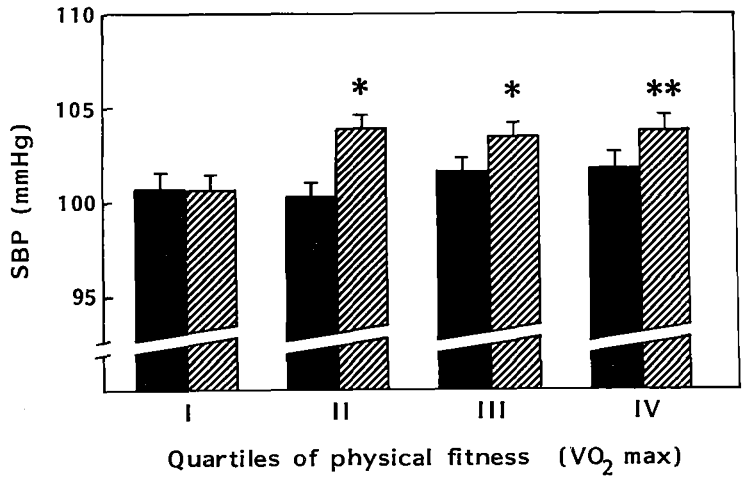

Figure 4.1.1. Mean levels of systolic blood pressure (SBP) with SEM by quartile of physical fitness (VO_2max in l/min). Adjustments are made for differences in age, skeletal age, height, body weight, and sum of four skinfolds. Quartiles I to IV present increasing levels of physical fitness. Dark bars indicate boys, arced bars indicate girls. * $p < 0.01$ *vs quartile I;* ** $p = 0.02$ *vs quartile I.*

Discussion

This study demonstrates that diastolic blood pressure is inversely related to physical fitness in children. Boys and girls with the highest levels of physical fitness showed the lowest diastolic blood pressure levels. No linear association between systolic blood pressure and physical fitness could be found. Body size is an important confounder of the association between blood pressure and physical fitness and should be taken into account to correctly interpret this association.

Determination of blood pressure is difficult, especially in children, due to its indirect measurement, intraindividual variation and because blood pressure levels change in association with growth and development (23-25). In this study, blood pressure was measured four times at two different occasions by trained paramedical observers. The first measurement may reflect a more labile blood pressure, thus presenting the influence of the sympathetic nervous system, which can be an important intermediate factor (26). Nonetheless, the difference between the mean blood pressure levels of both examinations was fairly constant and the last two blood pressure measurements appeared to be lower than the first two. Therefore, the mean of the

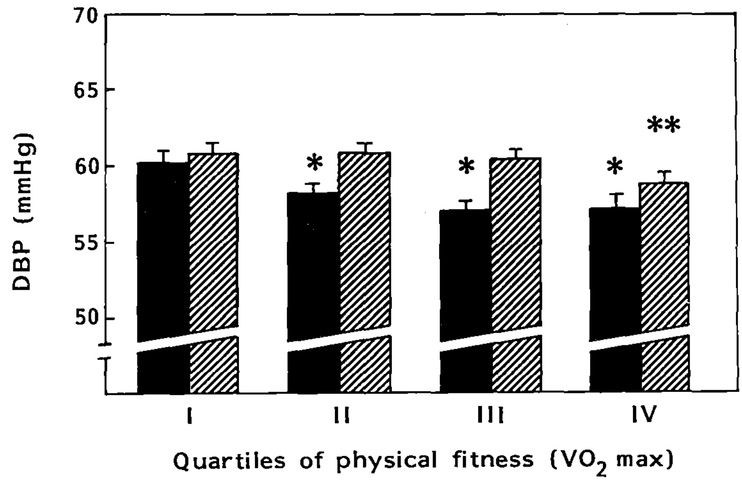

*Figure 4.1.2. Mean levels of diastolic blood pressure (DBP) with SEM by quartile of physical fitness (VO_2max in l/min). Adjustments are made for differences in age, skeletal age, height, body weight, and sum of four skinfolds. Quartiles I to IV present increasing levels of physical fitness. Dark bars indicate boys, arced bars indicate girls. * $p < 0.05$ vs quartile I; ** $p = 0.05$ vs quartile II.*

last two measurements was used in the analyses. Blood pressure measurements were performed with a random zero sphygmomanometer, chosen to reduce observer bias (27).

Physical fitness is usually determined submaximally and indirectly. In this study aerobic capacity was measured directly and with a maximal protocol. There is general agreement that the best method for maximal exercise testing in children below 10 years is a treadmill test (28). The Bruce test was chosen, because in this workload protocol the speed is variable so that even young children may perform the test without difficulty. In addition, reproducibility among children is high (29). Generally accepted criteria for reaching maximal exercise levels were used (30). Values of maximal oxygen uptake were within the ranges of data reported by Saris who used the same exercise protocol in a Dutch population, although boys in the present study had somewhat lower values (31). The explanation of this difference might be the exclusion in the study of Saris of those subjects who did not reach a respiratory quotient of 1.1

and the small sample size of his study population. Several other studies reported mean levels of maximal oxygen uptake similar to our values (32-34).

Although previous studies mostly used indirect measures of physical fitness and in general concerned older study populations, this study largely confirms the results of observational studies on blood pressure and physical fitness in youngsters. In some studies only lower levels of either systolic or diastolic blood pressure with increasing levels of fitness in boys were found (11,13,15), while others reported lower levels of systolic as well as diastolic blood pressure in both boys and girls (12,14).

Body weight and related parameters must be considered important confounding factors (16,35). The univariate correlation coefficients showed this clearly. An inverse association between diastolic blood pressure and physical fitness appeared in the linear regression analysis of blood pressure on maximal aerobic capacity and in the analysis by quartiles of physical fitness, after adjustments were made for body weight, height and sum of four skinfolds. This seems to result from a strong positive association of body size with both blood pressure and maximal aerobic capacity. By contrast, no clear relation between systolic blood pressure and physical fitness could be found after anthropometric characteristics were taken into account. The reduced mean level of systolic blood pressure in the lowest quartile of physical fitness in girls remains difficult to explain.

Several mechanisms of blood pressure reduction associated with repeated physical exercise are plausible. An increase in physical fitness could exert an increase of cardiac wall dimensions and mass (36). A lower heart rate and an increased stroke volume may follow (37). In our study pulse rate showed an inverse correlation with physical fitness. Also, in a linear regression analysis the relation between blood pressure and physical fitness decreased in strength after pulse rate was added to the model, which could be compatible with an intermediate role. On the other hand, pulse rate has been used in several studies as an indicator of physical fitness. Consequently, overadjustment could result from combining both maximal oxygen capacity and pulse rate in one model. With increasing physical fitness peripheral muscle development may occur, leading to an increase in absolute number of collateral blood vessels and vasodilatation, and resulting in a decrease of total peripheral resistance (38). Body weight may be reduced on regular physical exercise (39). Yet, some studies have shown that exercise lowers blood pressure without resulting in weight loss or a reduction in body fat (40,41). Regular exercise may lead to loss of water and electrolytes through transpiration and respiration. Indirectly, changes in dietary habits could accompany an altered life style with an increased physical fitness. Both processes could modulate the intake or excretion of sodium, potassium and other blood pressure related micronutrients (42,43). Chronic exercise training may reduce the levels of plasma norepinephrine and cortisol (44,45). In addition, other studies demonstrated an upregulation of the beta-adrenoreceptors after intervention of physical fitness in the vessel wall thus potentially relaxing the vascular wall tonus (46,47). Through exercise insulin sensitivity can be raised and the insulin-glucose ratio can be changed, which may favorably affect blood pressure levels (48,49). Finally, a reduction of blood pressure might occur by a changed stress response elicited by exercise training (50).

In summary, there are many potential mechanisms for a blood pressure lowering effect of an increased aerobic capacity. This study demonstrates that already at a young age an increasing physical fitness is associated with lower diastolic blood pressure levels.

Acknowledgement

We would like to thank all children, their parents and schoolteachers, who participated with so much enthusiasm in this study. The authors acknowledge Hanneke van Meurs, Anneke van der Muil-Houwing, Ria Rijneveldshoek, and Wilma Verbruggen for their dedicated work at the schools and at the research center. In addition, we would like to thank Theo Hartman, Diena Halbertsma, Monique Bekkenutte, Karin Eitjes, Ton Gremmen, Thea Wesseling, Clasien Schakenraad, Els Dozeman, Ellen van Steekelenburg and Hans Rijsenbrij of the Faculty of Human Movement Sciences, Amsterdam for their invaluable contribution in performing the exercise tests. This work was supported by grant nr. 28-1251 from the Netherlands Prevention Fund.

References

1. Five-year findings of the hypertension detection and follow-up program: Mortality by race-sex and age. JAMA 1979;242:2572-7.
2. Deubner DC, Tyroler HA, Cassel JC, Hames CG, Becker C. Attributable risk, population attributable risk, and population attributable fraction of death associated with hypertension in a biracial population. Circulation 1975;52:901-8.
3. Kannel WB, Stokes III J. Hypertension as a cardiovascular risk factor. In: Bulpitt CJ, ed. Epidemiology of Hypertension, Volume 6. Amsterdam, Elsevier; 1985:15-34.
4. Voors AW, Webber LS, Berenson GS. Time course studies of blood pressure in children:the Bogalusa heart study. Am J Epidemiol 1979;109:320-34.
5. Lauer RM, Clarke WR, Beaglehole R. Level, trend and variability of blood pressure during childhood: The Muscatine Study. Circulation 1984;69:242-9.
6. Hofman A, Valkenburg HA, Maas J, Groustra FN. The natural history of blood pressure in childhood. Int J Epidemiol 1985;14:91-6.

7. Gyntelberg F, Meyer J. Relationship between blood pressure and physical fitness, smoking and alcohol consumption in Copenhagen males aged 40-59. Acta Med Scand 1974;1975:375-80.
8. Cooper KH, Pollock ML, Martin RP, White SR, Linnerud AC, Jackson A. Physical fitness versus selected coronary risk factors: A cross-sectional study. JAMA 1976;236:166-9.
9. Boyer JL, Kasch FW. Exercise therapy in hypertensive men. JAMA 1970;211:1668-71.
10. Wilcox RG, Bennett T, Brown AM, MacDonald IA. Is exercise good for high blood pressure? Br Med J 1982;285:767-9.
11. Sallis JF, Patterson TL, Buono MJ, Nader PR. Relation of cardiovascular fitness and physical activity to cardiovascular disease risk factors in children and adults. Am J Epidemiol 1988;127:933-41.
12. Hofman A, Walter HJ, Connelly PA, Vaughan RD. Blood pressure and physical fitness in children. Hypertension 1987;9:188-91.
13. Panico S, Celentano E, Krogh V, Jossa F, Farinaro E, Trevisan M, Mancini M. Physical activity and its relationship to blood pressure in school children. J Chron Dis 1987;40:925-30.
14. Tell GS, Vellar OD. Physical fitness, physical activity and cardiovascular disease risk factors in adolescents: The Oslo Youth study. Prev Med 1988;17:12-24.
15. Fraser GE, Phillips RL, Harris R. Physical fitness and blood pressure in schoolchildren. Circulation 1983;67:405-12.
16. Fripp RR, Hodgson JL, Kwiterovich PO, Werner JC, Shuler HG, Whitman V. Aerobic capacity, obesity, and atherosclerotic risk factors in male adolescents. Pediatrics 1985;75:813-8.
17. Wilson SL, Gaffney FA, Laird WP, Fixler DE. Body size, composition, and fitness in adolescents with elevated blood pressures. Hypertension 1985;7:417-22.
18. Durnin JVGA, Rahaman MM. The assessment of the amount of fat in the human body from measurements of skinfold thickness. Br J Nutrition 1967;21:681-9.
19. Wright BM, Dore CF. A random-zero sphygmomanometer. Lancet 1970;i:337-8.
20. Tanner JM, Whitehouse RH, Marshall WA, Healy MJR, Goldstein H. Assessment of skeletal maturity and prediction of adult height (TW2 method), London: Academic Press; 1975.
21. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973;85:546-62.
22. Åstrand PO. Experimental studies of physical working capacity in relation to sex and age, Copenhagen: Munksgaard; 1952:29-38.
23. Whincup PH, Cook DG, Shaper AG. Blood pressure measurement in children: the importance of cuff bladdder size. J Hypertension 1989;7:845-50.
24. Report of the Second Task Force on blood pressure control in children-1987. Pediatrics. 1987;79:1-25.
25. Man de SA, André JL, Bachmann H, Grobbee DE, Ibsen KK, Laaser U, Lippert P, Hofman A. Blood pressure in childhood: pooled findings of six European studies. J Hypertension 1991;9:109-14.

26. Péronnet F, Cleroux J, Perrault H, Cousineau D, Champlain de J, Nadeau R. Plasma norepinephrine responses to exercise before and after training in humans. J Appl Physiol 1981;51:812-5.
27. Rose GA, Holland WW, Crowley EA. A sphygmomanometer for epidemiologists. Lancet 1964;i:296-300.
28. WHO. Excercise tests in relation to cardiovascular function, Geneva: Technical Report Series; 1968; 338.
29. Cumming GR, Everatt D, Hastman L. Bruce treadmill test in children: normal values in a clinic population. Am J Cardiol 1978;41:69-75.
30. Bar-Or O. Procedures for exercise testing in children. In: Katz M, Stiehm ER, eds. Pediatric sports medicine for the practitioner, New York: Springer-Verlag; 1983:305-41.
31. Saris WHM. Reference values for aerobic power of healthy 4- to 18-year-old Dutch children: Preliminary results. In: Binkhorst RA, Kemper HCG, Saris WHM, eds. Children and Exercise XI, Champaign: Human Kinetics Books;1985:151-60.
32. Rutenfranz J, Andersen KL, Seliger V, Klimmer F, Berndt I, Ruppel M. Maximal aerobic power and body composition during puberty growth period: similarities and differences between children of two European countries. Eur J Pediatr 1982;139:106-12.
33. Ikai M, Kitagawa K. Maximal oxygen uptake in Japanese related to sex and age. Med Sci Sports Exercise 1972;4:127-31.
34. Davies CTM, Barnes C, Godfrey S. Body composition and maximal exercise performance in children. Human Biol 1972;44:195-214.
35. Havlik RJ, Hubert HB, Fabsitz RB, Feinleib M. Weight and hypertension. Ann Int Med 1983;98:855-9.
36. Allen HD, Goldberg SJ, Sahn DJ, et al. A quantitative echocardiography study of champion swimmers. Circulation 1977;55:142-5.
37. Bar-Or O, Zwiren LD. Physiological effects of increased frequency of physical education classes and of endurance conditioning on 4- to 10-year old girls and boys. In: Bar-Or O, ed. Pediatric Work Physiology Natanya; 1973:183-98.
38. Sannerstedt R, Wasir H, Henning R, et al. Systemic haemodynamics in mild arterial hypertension before and after physical training. Clin Sci Molec Med 1973;45:145s-9s.
39. Reeves RS, Foreyt JP, Darnell LS, et al. Effects of exercise and dietary restriction on body weight of overweight adults. Med Sci Sports Exercise 1986;18:S9.
40. Krotkiewski M, Mandroukas K, Sjostrom L, et al. Effects of long-term physical training on body fat, metabolism and blood pressure in obesity. Metabolism 1979;28:650-8.
41. Hagberg JM, Goldring D, Ehsani AA, et al. Effect of exercise training on the blood pressure and hemodynamic features of hypertensive adolescents. Am J Cardiol 1983;52:763-8.
42. Luft FC, Weinberger MH. Sodium intake and essential hypertension. Hypertension 1982;4:III14-9.
43. McCarron DA, Stanton J, Henry H, et al. Assessment of nutritional correlates of blood pressure. Ann Intern Med. 1983;98:715-719.
44. Hartley LH MAson JW, Hogan RP, et al. Multiple hormonal responses to prolonged

exercise in relation to physical training. J Appl Physiol 1972;33:607-10.
45. Duncan JJ, Farr JE, Upton SJ, Hagan RD, Oglesby ME, Blair SN. The effects of aerobic exercise on plasma cathecholamines and blood pressure in patients with mild essential hypertension. JAMA 1985;254:2609-13.
46. Lehmann M, Dickhuth HH, Schmid P, Porzig H, Keul J. Plasma catecholamines, beta-adrenergic receptors, and isoproterenol sensitivity in endurance trained and non-endurance trained volunteers. Eur J Appl Physiology 1984;52:362-9.
47. Maki T, Kontula K, Myllynen P, Harkonen M. Beta-adrenergic receptors of human lymphocytes in physically active and immobilized subjects: characterization by a polyethylene glycol precipitation assay. Scan J Clin and Lab Investigation 1987;47:261-7.
48. Rauramaa R. Relationship of physical activity, glucose tolerance, and weight management. Prev Med 1984;13:37-46.
49. Ferrari P, Weidmann P. Insulin, insulin sensitivity and hypertension. J Hypertension 1990;8:491-500.
50. Holmes DS, Roth DL. Influence of aerobic fitness on pulse rate and subjective response to stress. Psychophysiology 1985;22:525-9.

4.2 BLOOD PRESSURE, PHYSICAL FITNESS AND HEMODYNAMIC CHARACTERISTICS IN CHILDHOOD

Introduction

Primary hypertension, an important risk factor for the occurrence of cardiovascular disease, may have its roots in childhood (1). Pathophysiological mechanisms, and in particular hemodynamic mechanisms related to the early state of an increased blood pressure, have been studied extensively. Two hypotheses on hemodynamics and blood pressure in childhood prevail (2-4). According to the first one, in the early state of primary hypertension a phase of high cardiac output gives rise to a secondary increase in peripheral vascular resistance. The second hypothesis proposes that a primarily increased peripheral resistance underlies the elevated pressure.

It has been suggested that increases in physical fitness may improve cardiovascular health and may favorably affect blood pressure. From the viewpoint of early prevention the hemodynamic characteristics of physical fitness and the hemodynamic mechanisms of an increased blood pressure in youngsters need more investigation.

This study was initiated to assess the hemodynamic determinants of blood pressure and the hemodynamic correlates of physical fitness early in life. Blood pressure and physical fitness were measured in a population of 1,558 Dutch schoolchildren, aged 7-11 years. In a subset of 1,081 children cardiac hemodynamic factors were assessed by echocardiography.

Methods

Population

A population of 1,774 schoolchildren, aged 7-11 years and residents of the town Zoetermeer, were invited for participation in a study on cardiovascular disease risk indicators and physical fitness. These children were all 3rd and 4th graders of a random sample of 28 schools out of 44 primary schools in Zoetermeer, a town of about 86,500 inhabitants, in the Netherlands. Data were collected at two examinations, a first one at the schools and a second one at a research center. At the first examination 1,613 children participated in the study (91%). One week after the school examination 1,558 (757 boys and 801 girls) children visited the research center for a second examination, resulting in a response rate at the combined two examinations of 88%.

Blood pressure, anthropometry and skeletal age

During the study period from March 1987 until June 1988 the following variables were measured: height, body weight, sum of four skinfolds, blood pressure, pulse rate at rest, skeletal age, maximal oxygen consumption, maximal heart rate, respiratory quotient and echocardiographic characteristics.

At the school examination height and body weight were measured with the children wearing indoor clothes and no shoes. Thickness of four skinfolds (biceps, triceps, subscapular, supra-iliac) was measured by a Holtain caliper (5).

Blood pressure was measured with a random-zero sphygmomanometer in sitting position on the left arm (6). Two measurements were taken, separated by a count of the pulse rate. The fifth Korotkoff phase was used as a measure of diastolic blood pressure. At the second examination blood pressure was remeasured by the same observer in the same way. In the analysis the average of the two blood pressure readings from the second examination was used.

Skeletal age was determined by a radiograph of the left hand. The radius, ulna and short finger bones, were used to assign a maturity score according to Tanner et al (7). All radiographs were read by one paramedical observer. No values of skeletal age were measured in 93 children (55 girls) either because the parents did not allow to make a radiograph of the hand or because the children moved their hand during the uptake.

Physical fitness

Physical fitness, defined as maximal aerobic capacity, was determined directly by measuring maximal oxygen consumption (VO_2max) during the Bruce treadmill test (8-12). Heart rate was calculated from a continuous ECG recording. Primary criteria for reaching maximal exercise were leveling off of oxygen uptake (i.e., no increase or less than 2 ml/kgmin) and/or leveling off of the heart rate despite an increased workload. Secondary criteria were a maximal respiratory gas exchange ratio greater than 1.0 and a maximal heart rate higher than the mean maximal heart rate minus two times the standard deviation, as given by Åstrand (12) for the corresponding age.

As part of the first examination, the parents completed a questionnaire on the medical history of their children. Based on this information 85 children were excluded from the exercise test for medical reasons. In four children multiple supraventricular ectopic beats appeared during exercise and consequently the test had to be stopped. A total of 149 children (10%) did not meet the criteria for reaching maximal exercise (n=71), or they did not follow the protocol correctly (n=78), and their data have not been used in the analysis. Consequently, complete data on physical fitness are available for 1,320 children. Mean values of chronological age, anthropometric variables and blood pressure were similar in the children who were excluded from the analysis and those who did reach maximal aerobic capacity.

Echocardiographic measurements

Because logistic restraints precluded the possibility of cardiac measurements in all participating children, hemodynamic measurements were carried out in a random sample of 1,081 children (549 girls and 532 boys) by one observer via two-dimensional and M-mode echocardiography in supine left lateral position at six consecutive cardiac cycles. Cardiac dimensions, including the maximal diameter of the aortic root (AO), end-diastolic interventricular septum thickness (IVS), maximal left atrial dimension (LAD), posterior left ventricular wall thickness (LVPW), end-systolic posterior left ventricular wall thickness (LVPW-S), end-diastolic left ventricular diameter (LVED), end-systolic left ventricular diameter (LVES), right ventricular diameter (RV), were obtained directly from the M-mode echocardiogram. Left ventricular mass (LVM) was calculated according to the formula $[(LVED+IVS+LVPW)^3 - LVED^3]x1.05$ (13). Left ventricular mass index (LVMI) was obtained by dividing left ventricular mass by body surface area (14). Cardiac output (CO) was derived from quantitative analysis, i.e., the mean of six consecutive cardiac cycles, by the area-length method (15) based on the parasternal short axis, apical long axis and four chamber views in 376 girls and 415 boys. Missing values resulted from failure to get a properly qualified view on which calculations could be based. Cardiac index (CI) was calculated by dividing cardiac output by body surface area. Stroke volume (SV) was obtained by dividing cardiac output by the mean heart rate, derived from the six cardiac cycles. Total peripheral resistance (TPR) was calculated by dividing mean arterial pressure by cardiac index. Heart rate was derived as the mean of the heart frequency during six cardiac cycles in echocardiography. The blood pressure, anthropometric and physical fitness values from the group of children of whom no hemodynamic characteristics were obtained, were similar to the values of the remaining group of children.

Data-analysis

The analysis was restricted to the 1,081 children in whom echocardiographic characteristics were obtained. The data-analytic approach was threefold.

Firstly, in order to establish average values of cardiac dimensions and derived measures in categories of the blood pressure distribution, mean levels of echocardiographic characteristics were computed by quartiles of blood pressure. Levels were adjusted for chronological age, skeletal age, height, body weight and sum of four skinfolds, which were viewed as potential confounders. Mean levels of cardiac index by blood pressure were adjusted for chronological age and skeletal age alone. The analyses were performed for systolic and diastolic blood pressure, separately for boys and girls. In boys cut-off points were 95, 100 and 106 mmHg for systolic blood pressure and 52, 58 and 63.5 for diastolic blood pressure. In girls the cut-off points used were 96, 102 and 108 mmHg for systolic blood pressure and 54, 59 and 65 mmHg for diastolic blood pressure.

Secondly, mean levels of echocardiographic dimensions and derived measures were determined by quartiles of physical fitness in boys and girls, separately. In boys the cut-off points were 1.27, 1.43 and 1.59 l/min of VO_2max and in girls 1.14, 1.27 and 1.41 l/min of VO_2max. Adjustments were made for chronological age, skeletal age, height, body weight and sum of four skinfolds. The values of cardiac index, left ventricular mass and total peripheral resistance were adjusted for chronological and skeletal age only.

Thirdly, linear regression coefficients were determined for blood pressure on cardiac characteristics and physical fitness on echocardiographic factors. Adjustments were made for differences in chronological age, skeletal age, body weight, height and sum of four skinfolds, except for the values of cardiac index, left ventricular mass index and total peripheral resistance which were adjusted for chronological age and skeletal age only. The p-values of each regression coefficient, used as a test for trend, were added to the Tables 4.2.3-6.

Results

In Table 4.2.1 mean values of chronological age, skeletal age, anthropometric characteristics, physical fitness and blood pressure with standard deviations are shown for boys and girls separately.

Table 4.2.2 presents average values of cardiac dimensions and derived measures, for both genders. Left ventricular mass was higher in boys, left ventricular mass index and stroke volume were higher in girls.

In Table 4.2.3 mean levels of echocardiographic characteristics are presented according to quartiles of systolic and diastolic blood pressure in boys. Category I refers to a relatively low level of systolic or diastolic blood pressure and category IV to a relatively high level of systolic or diastolic blood pressure. The lowest end-systolic left ventricular diameter was observed in the highest quartile of systolic blood pressure.

Table 4.2.1. Chronological age, skeletal age, anthropometric characteristics, physical fitness, maximal heart rate, respiratory quotient and blood pressure in 532 boys and 549 girls, aged 7 to 11 years.

	Boys		*Girls*	
Number	532		549	
Chronological age (yrs)	8.3	(0.7)*	8.3	(0.6)
Skeletal age (yrs)	7.8	(1.5)	8.4	(1.3)
Height (cm)	133	(7)	133	(7)
Weight (kg)	28	(4)	28	(5)
Sum of 4 skinfolds (mm)	27	(12)	32	(13)
VO_2max (l/min)	1.46	(0.24)	1.31	(0.21)
VO_2max (ml/kgmin)	51.0	(6.2)	45.5	(5.5)
Maximal heart rate (beats/min)	205	(8)	208	(9)
Respiratory quotient	1.14	(0.10)	1.17	(0.10)
Systolic blood pressure (mmHg)	101	(9)	102	(9)
Diastolic blood pressure (mmHg)	58	(8)	59	(8)

* Values are means with standard deviation in parentheses

The highest end-systolic posterior left ventricular wall thickness, cardiac output and cardiac index were found in the highest quartile of systolic blood pressure. The lowest level of stroke volume was found in the third quartile of systolic blood pressure. Heart rate was higher with increasing levels of systolic blood pressure. Similarly, for diastolic blood pressure a lower stroke volume and a higher heart rate were observed in the higher quartiles.

Table 4.2.4 shows mean levels of echocardiographic characteristics by quartile of blood pressure for girls. As for boys, in the fourth quartile of systolic blood pressure end-systolic left ventricular diameter was lowest. End-systolic posterior left ventricular wall thickness enlarged with increasing levels of systolic blood pressure. Cardiac output and cardiac index were higher in the third and fourth blood pressure quartile as compared to the lowest quartiles of systolic blood pressure. Heart rate increased with increasing levels of systolic blood pressure. A lower stroke volume was observed with increasing levels of diastolic blood pressure, although not reaching statistically significance. Heart rate was highest in the fourth quartile of diastolic blood pressure.

The results of the regression analysis, used as a test for trend, confirmed the

Table 4.2.2. Cardiac dimensions and derived measures* in supine position determined by echocardiography in 532 boys and 549 girls, aged 7 to 11 years.

	Boys		*Girls*	
Dimensions				
LVED (mm)	40.5	(2.4)	39.2	(2.6)
LVES (mm)	25.2	(2.3)	24.3	(2.4)
LAD (mm)	25.0	(2.4)	24.1	(2.5)
AO (mm)	21.3	(1.7)	20.3	(1.7)
RV (mm)	16.9	(2.9)	16.1	(2.7)
IVS (mm)	6.7	(0.7)	6.5	(0.6)
LVPW (mm)	6.9	(0.7)	6.8	(0.7)
LVPW-S (mm)	10.7	(1.0)	10.5	(1.0)
Derived measures				
LVM (g)	96.6	(15.3)	89.1	(15.0)
LVMI (g/m^2)	94.0	(12.4)	86.8	(11.5)
CO (l/min)	2.2	(0.5)	2.1	(0.4)
CI (l/min/m^2)	2.2	(0.4)	2.1	(0.4)
SV (ml/stroke)	27	(6)	25	(5)
TPR (units)	33.7	(7.0)	35.6	(7.7)
Heart rate (beats/min)	84	(11)	87	(11)

Abbreviations: LVED = end-diastolic left ventricular diameter; LVES = end-systolic left ventricular diameter; LAD = maximal left atrial dimension; AO = maximal aortic root diameter; RV = right ventricular diameter; IVS = end-diastolic interventricular septum thickness; LVPW = posterior left ventricular wall thickness; LVPW-S = end-systolic posterior left ventricular wall thickness; LVM = left ventricular mass; LVMI = left ventricular mass index; CO = cardiac output; CI = cardiac index; SV = stroke volume; TPR = total peripheral resistance

* Values are means with standard deviation in parentheses

results, presented in Table 4.2.3 and 4.2.4, which were derived from the analysis on quartiles of blood pressure.

Table 4.2.5 presents mean levels of echocardiographic characteristics by quartile of physical fitness in boys. Category I corresponds to a relatively poor level of physical

Table 4.2.3. Echocardiographic characteristics+ by quartiles of systolic (SBP) and diastolic (DBP) blood pressure in boys.

	Quartiles of SBP (mmHg)								
	I		II		III		IV		p++
LVES (mm)	25.6	(0.2)	25.6	(0.2)	25.2	(0.2)	23.9	(0.2)**	<0.01
LVPW-S (mm)	10.5	(0.1)	10.6	(0.1)	10.6	(0.1)	11.0	(0.1)**	<0.01
CO (l/min)	2.21	(0.04)	2.23	(0.04)	2.19	(0.04)	2.40	(0.05)**	<0.01
CI (l/min/m^2)	2.18	(0.04)	2.18	(0.04)	2.13	(0.04)	2.34	(0.05)**	<0.01
SV (ml/stroke)	28.1	(0.5)	27.5	(0.5)	26.7	(0.5)*	27.4	(0.5)	ns
HR (beats/min)	80	(1)	82	(1)	84	(1)*	89	(1)**	<0.01
	Quartiles of DBP (mmHg)								
	I		II		III		IV		p
LVES (mm)	25.1	(0.2)	25.1	(0.2)	25.6	(0.2)	24.6	(0.2)	ns
LVPW-S (mm)	10.8	(0.1)	10.7	(0.1)	10.5	(0.1)*	10.7	(0.1)	0.07
CO (l/min)	2.25	(0.04)	2.23	(0.04)	2.23	(0.05)	2.30	(0.05)	ns
CI (l/min/m^2)	2.21	(0.04)	2.18	(0.04)	2.16	(0.05)	2.25	(0.04)	ns
SV (ml/stroke)	28.3	(0.4)	27.5	(0.5)	27.0	(0.5)*	26.6	(0.5)**	0.01
HR (beats/min)	80	(1)	82	(1)	85	(1)**	88	(1)**	<0.01

Abbreviations: LVES = end-systolic left ventricular diameter; LVPW-S = end-systolic posterior left ventricular wall thickness; CO = cardiac output; CI = cardiac index; SV = stroke volume; HR = heart rate; ns = not significant

+ Values are means with standard error in parentheses. Adjustments are made for differences in chronological age, skeletal age, height, weight, and sum of four skinfolds, except for the values of cardiac index (CI) which are adjusted for chronological age and skeletal age alone.

++ Test for trend; * $p < 0.05$ vs I; ** $p < 0.01$ vs I

Table 4.2.4. Echocardiographic characteristics+ by quartiles of systolic (SBP) and diastolic (DBP) blood pressure in girls.

	Quartiles of SBP (mmHg)								
	I		II		III		IV		p++
LVES (mm)	24.8	(0.2)	24.3	(0.2)*	24.3	(0.2)	23.7	(0.2)**	<0.01
LVPW-S (mm)	10.3	(0.1)	10.5	(0.1)	10.7	(0.1)**	10.7	(0.1)**	<0.01
CO (l/min)	2.03	(0.04)	2.10	(0.04)	2.23	(0.04)**	2.19	(0.05)*	<0.01
CI (l/min/m²)	2.03	(0.04)	2.10	(0.04)	2.22	(0.04)**	2.16	(0.05)*	<0.01
SV (ml/stroke)	24.6	(0.4)	24.4	(0.4)	25.8	(0.5)	23.8	(0.5)	ns
HR (beats/min)	83	(1)	87	(1)**	87	(1)**	92	(1)**	<0.01
	Quartiles of DBP (mmHg)								
	I		II		III		IV		p
LVES (mm)	24.4	(0.2)	24.3	(0.2)	24.3	(0.2)	24.1	(0.2)	ns
LVPW-S (mm)	10.6	(0.1)	10.4	(0.1)	10.6	(0.1)	10.6	(0.1)	ns
CO (l/min)	2.15	(0.04)	2.12	(0.04)	2.09	(0.04)	2.17	(0.05)	ns
CI (l/min/m²)	2.15	(0.04)	2.12	(0.04)	2.07	(0.04)	2.15	(0.05)	ns
SV (ml/stroke)	25.4	(0.4)	24.5	(0.4)	24.3	(0.4)	24.2	(0.5)	0.02
HR (beats/min)	86	(1)	87	(1)	88	(1)	90	(1)**	<0.01

Abbreviations: LVES = end-systolic left ventricular diameter; LVPW-S = end-systolic posterior left ventricular wall thickness; CO = cardiac output; CI = cardiac index; SV = stroke volume; HR = heart rate; ns = not significant

+ Values are means with standard error in parentheses. Adjustments are made for differences in chronological age, skeletal age, height, weight, and sum of four skinfolds, except for the values of cardiac index (CI) which are adjusted for chronological age and skeletal age alone.

++ Test for trend; * $p < 0.05$ vs I; ** $p < 0.01$ vs I

Table 4.2.5. Echocardiographic characteristics+ by quartiles of physical fitness in boys.

	Quartiles of physical fitness (VO_2 max in l/min)								
	I		II		III		IV		p^{++}
LAD (mm)	24.5	(0.3)	25.2	(0.2)*	25.0	(0.2)	25.4	(0.3)*	<0.01
LVED (mm)	40.4	(0.2)	40.5	(0.2)	40.6	(0.2)	40.9	(0.2)	ns
LVPW-S (mm)	10.3	(0.1)	10.7	(0.1)**	10.7	(0.1)**	10.9	(0.1)**	<0.01
LVM (g)	92.0	(1.5)	96.4	(1.2)*	97.4	(1.2)**	100.9	(1.4)**	<0.01
LVMI (g/m^2)	89.6	(1.3)	93.9	(1.2)*	93.9	(1.2)*	97.3	(1.3)**	<0.01
CO (l/min)	2.17	(0.06)	2.24	(0.05)	2.25	(0.05)	2.45	(0.06)**	<0.01
CI ($l/min/m^2$)	2.15	(0.05)	2.21	(0.04)	2.18	(0.05)	2.35	(0.05)*	<0.01
SV (ml/stroke)	25.7	(0.6)	27.3	(0.5)*	27.9	(0.5)**	29.7	(0.6)**	<0.01
TPR (units)	34.0	(0.8)	33.0	(0.8)	33.6	(0.8)	32.1	(0.8)	0.07
HR (beats/min)	86	(1)	84	(1)	83	(1)	82	(1)	0.05

Abbreviations: LAD = left atrial dimension; LVED= end-diastolic left ventricular diameter; LVPW-S = end-systolic posterior left ventricular wall thickness; LVM = left ventricular mass; LVMI = left ventricular mass index; CO = cardiac output; CI = cardiac index; SV = stroke volume, TPR = total peripheral resistance; HR = heart rate; ns = not significant

+ Values are means with standard error in parentheses. Adjustments are made for differences in chronological age, skeletal age, height, weight, and sum of four skinfolds, except for the values of cardiac index (CI), left ventricular mass index (LVMI) and total peripheral resistance (TPR) which are adjusted for chronological age and skeletal age alone.

++ Test for trend; * $p < 0.05$ vs I; ** $p < 0.01$ vs I

Table 4.2.6. Echocardiographic characteristics+ by quartiles of physical fitness in girls.

	Quartiles of physical fitness (VO_2 max in l/min)								
	I		II		III		IV		p++
LAD (mm)	23.6	(0.2)	24.3	(0.2)*	24.2	(0.2)	24.5	(0.2)*	0.01
LVED (mm)	38.5	(0.2)	39.2	(0.2)*	39.3	(0.2)*	40.1	(0.3)**	<0.01
LVPW-S (mm)	10.3	(0.1)	10.6	(0.1)*	10.4	(0.1)	10.8	(0.1)**	<0.01
LVM (g)	87.4	(1.3)	88.9	(1.2)	89.8	(1.1)	93.4	(1.4)**	0.01
LVMI (g/m^2)	83.9	(1.2)	85.7	(1.1)	87.7	(1.1)*	91.3	(1.2)**	<0.01
CO (l/min)	2.06	(0.05)	2.12	(0.05)	2.11	(0.05)	2.32	(0.06)**	0.05
CI ($l/min/m^2$)	2.07	(0.04)	2.11	(0.05)	2.10	(0.05)	2.25	(0.05)*	ns
SV (ml/stroke)	23.8	(0.4)	24.5	(0.5)	24.2	(0.4)	27.4	(0.6)**	<0.01
TPR (units)	35.9	(0.8)	36.1	(0.9)	36.1	(0.9)	33.9	(1.0)	ns
HR (beats/min)	87	(1)	87	(1)	88	(1)	86	(1)	ns

Abbreviations: LAD = left atrial dimension; LVED= end-diastolic left ventricular diameter; LVPW-S = end-systolic posterior left ventricular wall thickness; LVM = left ventricular mass; LVMI = left ventricular mass index; CO = cardiac output; CI = cardiac index; SV = stroke volume, TPR = total peripheral resistance; ns = not significant

+ Values are means with standard error in parentheses. Adjustments are made for differences in chronological age, skeletal age, height, weight, and sum of four skinfolds, except for the values of cardiac index (CI), left ventricular mass index (LVMI) and total peripheral resistance (TPR) which are adjusted for chronological age and skeletal age alone.

++ Test for trend; * $p < 0.05$ vs I; ** $p < 0.01$ vs I

fitness and category IV to a relatively high level. The highest left atrial dimension was found in the fourth quartile of physical fitness. With increasing levels of physical fitness increasing end-systolic posterior left ventricular wall thickness, left ventricular mass and left ventricular mass index were observed. The highest levels of cardiac output and cardiac index were found in the highest category of maximal aerobic capacity. An increase in stroke volume was observed with an increase in physical fitness. A decrease in calculated total peripheral resistance and heart rate was shown with increasing levels of physical fitness, although not statistically significantly.

In Table 4.2.6 mean echocardiographic dimensions and derived measures according to quartiles of physical fitness in girls are shown. The highest levels of left atrial dimension, end-systolic posterior left ventricular wall thickness, left ventricular mass, left ventricular mass index, cardiac output, cardiac index and stroke volume were found in the highest quartile of physical fitness.

The results of the analyses on quartiles of physical fitness presented in Table 4.2.5 and 4.2.6 were confirmed by the linear regression analysis.

Discussion

In our study end-systolic posterior left ventricular wall thickness, cardiac output and cardiac index are positively related to systolic blood pressure in 7 to 11 year old children. In addition, children with higher levels of physical fitness show a higher left atrial dimension, end-systolic posterior left ventricular wall thickness, left ventricular mass, left ventricular mass index, stroke volume, cardiac output, and cardiac index. Before we interpret these findings, some characteristics of the study must be addressed.

Results from measurements of cardiac dimensions and derived measures were quite similar to the results from other studies, although most studies report their cardiac values by weight, height or body surface area (16-18). Cardiac output was measured by the area-length method. This method is probably a more accurate measure of the volume of a three-dimensional cavity than the minor axis method in which the cubed end-diastolic and end-systolic left ventricular internal dimensions are used as an estimate of the left ventricular stroke volume (19,20). All cardiac measurements were performed by one trained paramedical observer.

Usually, higher levels of cardiac output in children with higher levels of blood pressure are reported from studies in which invasive methods to determine cardiac output were used (21-25). On the other hand, studies which reported no association between blood pressure and cardiac output, measured by echocardiography, concerned either a larger age range, including prepubertal and pubertal children, or cardiac output was measured with the minor axis method (26-30). Our findings are limited to systolic blood pressure and we were not able to study oxygen uptake in rest to identify those children with an elevated cardiac output and no difference in arteriovenous oxygen content (3,31). Nonetheless, our findings are compatible with the view that at the early state of an increased blood pressure in prepubertal youngsters a high cardiac output exists which may be followed by an increase in peripheral resistance through autoregulation.

Although some studies reported a higher left ventricular mass with increasing levels of blood pressure (26,27), in our study in relatively young children no clear relation could be found. Yet, an increase in end-systolic posterior left ventricular wall thickness was observed in children with higher systolic blood pressure. Burke et al. in the Bogalusa Heart Study also reported an increase in end-systolic posterior left ventricular wall thickness only, after adjustments for body size characteristics (30). They did not observe an increase in left ventricular mass, calculated according to several formula's, with an increasing systolic blood pressure. Burke et al. suggested that systolic wall thickness may be affected by changes in both chamber size and myocardial performance (30). An increase in posterior wall thickness from diastole to systole with an increased blood pressure may be indicative of an enhanced systolic myocardial performance. This increase in systolic wall thickness may represent an early consequence of elevated blood pressure in children. The decrease in end-systolic left ventricular diameter with increasing levels of systolic blood pressure could also reflect early myocardial changes in the ventricular wall due to an increased systolic blood pressure. Although not statistically significant, in a study of Schieken et al. a similar phenomenon was observed (26).

The findings of an increasing left ventricular wall mass indices, left atrial dimension and slightly increasing end-diastolic left ventricular diameter with increasing physical fitness confirms reports in adolescents (32-34). These results suggest the presence of concentric cardiac hypertrophy and a slightly increased volume in the left ventricle with comparative maintenance of the ratio of wall thickness to internal diameter, thus implying a normal wall stress. This is in contrast with our findings concerning an increased systolic blood pressure, which appeared to be related to an increase in posterior left ventricular wall thickness and a decrease in left ventricular diameter. Thus, an increased systolic blood pressure could result in an increased wall stress already at a young age. Concluding, a clearly different hemodynamic pattern can be observed between children with an increased blood pressure versus children with an increased physical fitness.

Stroke volume is higher with increasing levels of maximal aerobic capacity. Although studies in adolescents confirm this notion, in prepubertal children changes in stroke volume accompanied by increased physical condition have not been reported (35,36) An increased stroke volume may result from an increased contractility or an increased end-diastolic volume. Experimental evidence tends to support an increased end-diastolic volume as the most important factor (37).

A trend towards a reduction in heart rate was shown with increasing physical fitness. The mechanism of fitness related bradycardia is not clear. This may be secondary to an increase in stroke volume, but may also reflect a stronger parasympathetic and a diminished sympathetic drive (38).

In a previous report on the same study population higher levels of physical fitness were shown to be accompanied by lower levels of diastolic blood pressure (39). This could result from a lower total peripheral resistance mainly affecting diastolic blood pressure levels. However, as we could not demonstrate a clear decrease in total peripheral resistance with increasing levels of physical fitness, the nature of this association remains to be established.

In conclusion, the results of this study in young prepubertal children seem to support the presence of a hyperkinetic state in the early phase of an increased blood pressure. In addition, children with an increased physical fitness appear to have an increased left ventricular mass, larger left atrial diameter and a higher stroke volume compared to those who are less physically fit. These children also tend to have a lower heart rate and a reduced total peripheral resistance.

Acknowledgement

We are indebted to all children and their parents for their essential contribution to this study. The authors gratefully acknowledge Hanneke van Meurs for measuring all echocardiographic characteristics. We thank prof. Piet Verdouw, PhD, and prof. Rick Wilson, MD, for their useful comments.

References

1. Berenson GS, McMahan CA, Voors AW, et al.: Cardiovascular risk factors in children. The early natural history of atherosclerosis and essential hypertension. New York: Oxford University Press, 1980.
2. Birkenhäger WH, De Leeuw PW, Schalekamp MADH. Control mechanisms in essential

hypertension. Amsterdam, New York, Oxford: Elsevier Biomedical Press, 1982.
3. Lund-Johansen P. State of the art review. Haemodynamics in essential hypertension. Clin Sci 1980;59:343s-54s.
4. Folkow B. Physiological aspects of primary hypertension. Physiol Rev 1982;62:347-504.
5. Durnin JVGA, Rahaman MM. The assessment of the amount of fat in the human body from measurements of skinfold thickness. Br J Nutrition 1967;21:681-9.
6. Wright BM, Dore CF. A random-zero sphygmomanometer. Lancet 1970;i:337-8.
7. Tanner JM, Whitehouse RH, Marshall WA, Healy MJR, Goldstein H. Assessment of skeletal maturity and prediction of adult height (TW2 method). London: Academic Press, 1975.
8. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973;85:546-562.
9. WHO. Excercise tests in relation to cardiovascular function. Geneva: Technical Report Series, 1968;338.
10. Cumming GR, Everatt D, Hastman L. Bruce treadmill test in children: normal values in a clinic population. Am J Cardiol 1978;41:69-75.
11. Saris WHM. Aerobic power and daily physical activity in children. With special reference to methods and cardiovascular risk indicators. Thesis. Nijmegen: Krips Repro Meppel, 1982.
12. Åstrand PO. Experimental studies of physical working capacity in relation to sex and age. Copenhagen: Munksgaard, 1952.
13. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. Circulation 1977;55:613-8.
14. Dubois D, Dubois EF. A formulae to estimate the aproximate surface area if height and weight are known. Arch Int Med 1916;17:868-76.
15. Roelandt JTRC. Practical echocardiology. Chichester New York Brisbane Toronto: Research Studies Press, 1981;117-35.
16. Voogd PJ, Rijsterborgh H, Lubsen J, Arntzenius AC, Monsjou LK, Godijn EH. Reference ranges of echocardiographic measurements in the Dutch population. Eur Heart J 1984;5:762-70.
17. Henry WL, Ware J, Gardin JM. Echocardiographic measurements in normal subjects. Growth related changes that occur between infancy and early adulthood. Circulation 1978;57:278-85.
18. Lundstrom NR. Clinical applications of echocardiography in infants and children. Acta Paed Scand 1974;63:23-32.
19. Linhart JW, Mintz GS, Segal BL, Kawai N, Kotler NM. Left ventricular volume measurement by echocardiography: Fact or fiction. Am J Cardiol 1975;36:114-8.
20. Kronik G, Slany J, Mosslacher H. Comparative value of eight M-mode echocardiographic formulas for determining left ventricular stroke volume. Circulation 1979;60:1308-16.
21. Lund-Johansen P. Hemodynamics in early essential hypertension. Acta Med Scand 1967;suppl 482:1-101.
22. Safar M, Fendler JP, Wil B, Idatte JM, Beuve-Mery P, Milliez P. Etude hemodynamique

de l'hypertension arterielle labile. La Press Medicale 1970;78:111-4.
23. Julius S, Pascual AV, Sannerstedt R, Mitchell C. Relationship between cardiac output and peripheral resistance in borderline hypertension. Circulation 1971;43:382-90.
24. Jern S. Physiological and hemodynamic factors in borderline hypertension. Acta Med Scand 1982;suppl 662:1-54.
25. Saito T. Hemodynamics and the baroreflex function in borderline hypertension. Jpn Circ J 1983;47:221-9.
26. Schieken RM, Clarke WR, Lauer RM. Left ventricular hypertrophy in children with blood pressures in the upper quintile of the Distribution. The Muscatine Study. Hypertension 1981;3:669-75.
27. Zahka KG, Neill CA, Langford K, et al. Cardiac involvement in adolescent hypertension. Hypertension 1981;3:664-8.
28. Hofman A, Roelandt JTRC, Boomsma F, Schalekamp MADH, Valkenburg HA. Haemodynamics, plasma noradrenaline and plasma renin in hypertensive and normotensive teenagers. Clin Sci 1981;61:169-74.
29. Hofman A, Ellison RC, Newburger J, Miettinen O. Blood pressure and hemodynamics in teenagers. Br Heart J 1982;48:377-80.
30. Burke GL, Archilla RA, Culpepper WS, Webber LS, Chiang YK, Berenson GS. Blood pressure and echocardiographic measures in children: The Bogalusa Heart Study. Circulation 1987;75:106-14.
31. Lund-Johansen P. State of the art review. Haemodynamics in essential hypertension. Clin Sci 1980;59:343s-54s.
32. Longhurst JC, Kelly AR, Gonyea WJ, Mitchell JH. Chronic training with static and dynamic exercise. Cardiovascular adaptation and response to exercise. Circ Res 1981;48 suppl 1:171-8.
33. Allen HD, Goldberg SJ, Sahn DJ, Schy N, Wojcik R. A quantitative echocardiographic study of champion childhood swimmers. Circulation 1977;55:142-5.
34. Lengyel M, Gyarfas I. The importance of echocardiography in the assessment of left ventricular hypertrophy in trained and untrained schoolchildren. Acta Cardiologica 1979;2:63-9.
35. Hamilton P, Andrew GM. Influence of growth and athletic training on heart and lung functions. Eur J Appl Physiol 1976;36:27-38.
36. Lind AR. Cardiovascular responses to static exercise. Circulation 1970;41:173-6.
37. Blomqvist CG, Saltin B. Cardiovascular adaptations to physical training. Annu Rev Physiol 1983;45:169-89.
38. Eriksson BO, Koch G. Cardiac output and intra-arterial blood pressure at rest and during submaximal and maximal exercise in 11- to 13-year-old boys before and after physical training. In Bar-Or, ed. Pediatric Work Physiology. Wingate Institute, Natanya, 1973:139-50.
39. De Man SA, Grobbee DE, Valkenburg HA, Hofman A. Diastolic blood pressure is inversely related to physical fitness in children (submitted).

CHAPTER 5

PHYSICAL FITNESS, SERUM LIPIDS AND LIPOPROTEINS IN CHILDHOOD

5. PHYSICAL FITNESS, SERUM LIPIDS AND LIPOPROTEINS IN CHILDHOOD

Introduction

Serum lipid levels in adults are associated with the occurrence of cardiovascular diseases (CVD) (1-4). As autopsy studies have indicated, atherosclerosis begins in childhood and is related to serum lipids already at a young age (5,6). The study of determinants of serum lipids and lipoproteins in childhood may provide insight into the etiology of atherosclerotic vessel disease and indicate ways to prevention of CVD. From this perspective, the potential effect of physical fitness on the lipid and lipoprotein profile may be of great importance. An increase in physical fitness has been shown to induce beneficial changes of the levels of serum lipids and lipoproteins in adults (7-10). Results from observational studies on this issue in children are contradictory. There is evidence for an association between levels of serum cholesterol, lipoproteins and physical fitness in children (11-13), but there are also several studies indicating no relation between physical fitness and serum lipoproteins in childhood (14,15). Measuring physical fitness is difficult, especially in children, and the use of a more objective measure of fitness, such as a directly determined maximal aerobic capacity, may help to clarify the association between lipids and physical fitness. Also, data on apolipoproteins and physical fitness at a young age are almost completely lacking (16).

Therefore, to determine whether early in life physical fitness and serum lipids and lipoproteins are related, a population of 1,558 schoolchildren, aged 7-11 years and living in the Netherlands, was examined.

Materials and methods

Population

From March 1987 until June 1988 1,774 Dutch schoolchildren, aged 7-11 years and residents of the town Zoetermeer, were invited for participation in a study on CVD risk indicators and physical fitness. These children were all 3th and 4th graders from 28 schools, a random sample out of 44 primary schools in Zoetermeer, a town of about 86,500 inhabitants near the Hague in the Netherlands. The study was approved by the Medical Ethical Committee of the Erasmus University, Medical School. Informed consent was obtained from the parents.

Data were collected at two examinations, firstly at school and subsequently at a research center. During the first examination 1,613 children participated in the study (91 per cent). One week after the school examination 1,558 (757 boys and 801 girls) children visited the research center for a second examination, resulting in a response rate at the combined two examinations of 88 per cent.

Measurements

At the school examination, height and body weight were measured with the children wearing indoor clothes and no shoes. Thickness of skinfolds was measured with a Holtain caliper at four sites: biceps, triceps, subscapular and supra-iliac. The sum of four skinfolds was used as a criterion score for subcutaneous fat (17). Blood pressure was measured with a random zero sphygmomanometer in sitting position.

At the second examination at the research center blood samples were obtained from nonfasting subjects. Blood drawing was completed before the exercise test. An automated enzymatic procedure was used for determination of serum total cholesterol (18). High density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol were measured by the same method after precipitation. The phosphotungstate method according to Burstein and coworkers (19), with a minor modification as described by Grove (20), was used for precipitation of HDL. HDL cholesterol subfractions, HDL_2 and HDL_3, were determined by precipitation with Mn^{2+}-heparin and dextransulfate according to Gidez et al. (21). For LDL cholesterol, precipitation was carried out with polyvinyl sulphate. Apolipoproteins A-I and B were assayed by an automated immunoturbidimetric method (Kone Diagnostics Finland). Apolipoprotein A-II was determined by radial immunodiffusion against specific antiserum according to Cheung and Albers, with slight modifications (22). The determinations of all lipids and lipoproteins were carried out in the laboratory of our department. For serum total cholesterol, HDL cholesterol, apolipoprotein A-I and B our laboratory participates in the Lipid Standardization Program of the WHO Regional Lipid Reference Centre in Prague (Dr. D. Grafnetter). The number of children, from whom serum total, LDL and HDL cholesterol and all apolipoproteins were determined, varied from 90 to 95 per cent of the total number of 1,558 children participating. For the subfractions HDL_2 and HDL_3 cholesterol the number of missing values was 14 per cent in girls and 15 per cent in boys. In case of a small quantity of collected serum, priority was given to the determination of total cholesterol and other lipoproteins rather than the subfractions of HDL cholesterol.

A radiograph of the left hand was made to assess skeletal age. A maturity score to each bone stage was assigned according to Tanner et al. (23). The 13 bones, comprising the radius, ulna and short finger bones, were used to determine skeletal age. All radiographs were read by one observer. In 93 children (55 girls) no values of skeletal age were obtained either because the parents did not allow to make a radiograph of the hand or because the children moved their hand during the exposure.

Physical fitness, defined as maximal aerobic capacity, was determined directly by measuring maximal oxygen consumption (VO_2max) during the Bruce treadmill test. According to this protocol, the speed as well as the gradient are increased every 3 minutes (24). Heart rate was calculated from a continuous ECG recording. The criteria for reaching maximal exercise were leveling off of oxygen uptake (i.e., no increase or less than 2 ml/kgmin) and/or leveling off of the heart rate despite an increased workload. Further criteria used for the determination of a reached maximal exercise test included a maximal respiratory gas exchange ratio greater than 1.0 and a maximal heart rate higher than the mean maximal heart rate minus two times the standard deviation, as given by Åstrand (25) for the corresponding age. As part of the first examination, the parents completed a questionnaire on the medical history of their children. On the basis of this information 85 children were excluded from the exercise test for the following reasons: asthma and chronic bronchitis (73), congenital heart disease (4), epilepsy (2), lung dysplasia (1), choanal atresia (1), diseases of the muscular and skeletal system (4). In 4 children premature ventricular beats appeared on exercise and consequently the test was stopped.

A total of 149 children (10 per cent) did not meet the criteria for reaching maximal exercise (71 subjects) or did not follow the protocol correctly (78 subjects) and their data have not been used in the analysis. Mean values of age, anthropometric variables and of serum lipids and lipoproteins were similar in the children who did and those who did not reach a maximal exercise level.

Data Analysis

The data analysis focused on the association between physical fitness as assessed by the maximal treadmill test and serum lipids and lipoproteins. Firstly, serum lipid levels were compared according to quartiles of physical fitness, expressed in liters of VO_2max per minute, for boys and girls separately. Cut-off points were 1.29, 1.44 and 1.61 liter/min of VO_2max for boys, and 1.16, 1.29 and 1.42 liter/min for girls. Average values of serum cholesterol and lipoproteins were computed by quartiles of physical fitness, adjusted for differences in age, skeletal age, body weight, height and sum of four skinfolds.

Subsequently, in order to analyze the linear relation between physical fitness and serum lipids, a gender-specific linear regression model was used with serum lipids and lipoproteins as the dependent variables. Physical fitness, as independent variable, was expressed in absolute terms (VO_2max in l/min) and age, skeletal age, body weight, height and sum of four skinfolds were added to the model as potential confounders.

Finally, differences in serum lipids and lipoproteins were studied between children with a relatively high level versus lower levels of physical fitness. For this purpose a multiple linear regression model was used in which serum lipids and lipoproteins were the outcome variables and indicator variables for the two categories of physical fitness served as independent variables. Maximal oxygen consumption below the 90th centile was used as reference category. In this way the presented regression coefficients showed the difference in serum lipid and lipoprotein levels between children at or above the upper decile of the distribution of physical fitness and below the 90th centile. Cut-off points were 1.75 liter/min of VO_2max for boys and 1.57 liter/min for girls. Adjustments were made for age, skeletal age, body weight, height and sum of four skinfolds.

Results

In Table 5.1 age, skeletal age, anthropometric characteristics, parameters of physical fitness, serum lipids and lipoproteins of the study participants are given. Due to exclusion of some participants and missing values, the total numbers of skeletal age, measured skinfolds and maximal exercise parameters differ slightly from the grand totals mentioned in the table. Also, mean levels of serum cholesterol and lipoprotein numbers are based on slightly different numbers, because of missing values. The mean sum of four skinfolds was higher in girls. Maximal oxygen consumption in l/min and per kg body weight was higher in boys. Total cholesterol, LDL cholesterol and apolipoprotein B levels were higher in girls than in boys.

Table 5.2 shows mean levels of total, LDL, HDL cholesterol and the subfractions HDL_2 and HDL_3 cholesterol in four categories of increasing maximal aerobic capacity. Mean levels and standard errors are adjusted for age, skeletal age, weight, height, and sum of four skinfolds. In boys mean total cholesterol reached a somewhat higher level in the third category of aerobic capacity, although not significantly. In girls a non-significant lower level of total cholesterol was observed in the upper twentyfive per cent of physical fitness. No difference in mean LDL cholesterol, HDL cholesterol levels or its subfractions was observed across the quartiles of physical fitness neither in boys nor in girls.

Figure 5.1 shows mean levels of serum apolipoproteins by quartile of physical fitness, for boys and girls separately. The levels were adjusted for differences in age, skeletal age, weight, height and sum of four skinfolds. No differences were found in apolipoprotein A-I levels between the four groups of physical fitness in both sexes. In

Table 5.1. Age, skeletal age, anthropometric characteristics, physical fitness, maximal heart rate, serum lipids and lipoproteins* for boys and girls.

	Boys			Girls		
	n	*Mean*	*(SD)*	*n*	*Mean*	*(SD)*
Age (yrs)	757	8.4	(0.7)	801	8.4	(0.7)
Skeletal age (yrs)	719	7.9	(1.4)	746	8.4	(1.3)
Height (cm)	757	133.9	(6.8)	801	133.4	(6.6)
Weigh (kg)	757	28.6	(4.5)	801	28.8	(4.9)
Sum of 4 skinfolds (mm)	752	26	(11)	796	33	(13)
VO_2max (l/min)	631	1.46	(0.24)	689	1.31	(0.21)
VO_2max (ml/kgmin)	631	51.0	(6.2)	689	45.5	(5.5)
Maximal heart rate (b/min)	631	205	(8)	689	208	(9)
Total cholesterol (mg/dl)	718	176	(27)	746	182	(30)
LDL cholesterol (mg/dl)	693	101	(27)	717	107	(31)
HDL cholesterol (mg/dl)	705	51	(11)	735	50	(11)
HDL_2 cholesterol (mg/dl)	643	16	(8)	691	15	(8)
HDL_3 cholesterol (mg/dl)	643	35	(6)	691	35	(6)
Apolipoprotein A-I (mg/dl)	703	137	(18)	727	136	(18)
Apolipoprotein A-II (mg/dl)	704	48	(7)	733	47	(7)
Apolipoprotein B (mg/dl)	703	69	(14)	727	72	(16)

* Values are means with standard deviations in parentheses

boys a significantly higher level of apolipoprotein A-II was seen with an increasing level of physical fitness. For apolipoprotein B in boys and girls no differences were observed, although non-significantly lower levels were present in the second to fourth category compared to the lowest category of maximal aerobic capacity in girls.

In the Tables 5.3 and 5.4 linear regression coefficients of lipids and lipoproteins on physical fitness in boys and girls are given. Adjustments were made firstly for age and secondly for age, skeletal age, weight, height and sum of four skinfolds. Adding anthropometric characteristics and skeletal age to the model did hardly affect the regression coefficients of serum lipids and lipoproteins on maximal aerobic capacity, although height and the sum of skinfolds appeared to be related with the lipoprotein profile in both boys and girls. Only in boys a positive association between serum apolipoprotein A-II and physical fitness was seen after adjustment for age, skeletal age

Table 5.2. Serum lipids and lipoproteins* (in mg/dl) by categories according to quartiles of physical fitness (VO_2max in l/min) in boys and girls aged 7 to 11 years. Adjustments were made for differences in age, skeletal age, height, weight, and sum of four skinfolds.

	Quartiles of physical fitness (VO_2 max in l/min)⁺							
	I		II		III		IV	
Boys								
n	138		141		145		144	
Total cholesterol (mg/dl)	174	(2.7)	177	(2.2)	179	(2.2)	175	(2.6)
LDL cholesterol (mg/dl)	101	(2.8)	103	(2.3)	102	(2.3)	100	(2.8)
HDL cholesterol (mg/dl)	53	(1.1)	51	(0.9)	53	(0.9)	51	(1.1)
HDL_2 cholesterol (mg/dl)	17	(0.9)	16	(0.7)	17	(0.7)	16	(0.8)
HDL_3 cholesterol (mg/dl)	36	(0.7)	36	(0.6)	35	(0.5)	36	(0.6)
Girls								
n	151		150		149		158	
Total cholesterol (mg/dl)	181	(2.9)	184	(2.5)	183	(2.5)	179	(3.0)
LDL cholesterol (mg/dl)	106	(3.1)	110	(2.6)	109	(2.6)	106	(3.1)
HDL cholesterol (mg/dl)	50	(1.1)	52	(0.9)	52	(0.9)	50	(1.0)
HDL_2 cholesterol (mg/dl)	15	(0.8)	15	(0.7)	16	(0.6)	14	(0.8)
HDL_3 cholesterol (mg/dl)	36	(0.6)	36	(0.5)	36	(0.5)	35	(0.6)

* Values are mean levels with standard errors between parentheses

⁺ Category I refers to poor and category IV to high physical fitness. The 25th, 50th, 75th centiles were for boys 1.29, 1.44 and 1.61 l/min and for girls 1.16, 1.29 and 1.42 l/min, respectively.

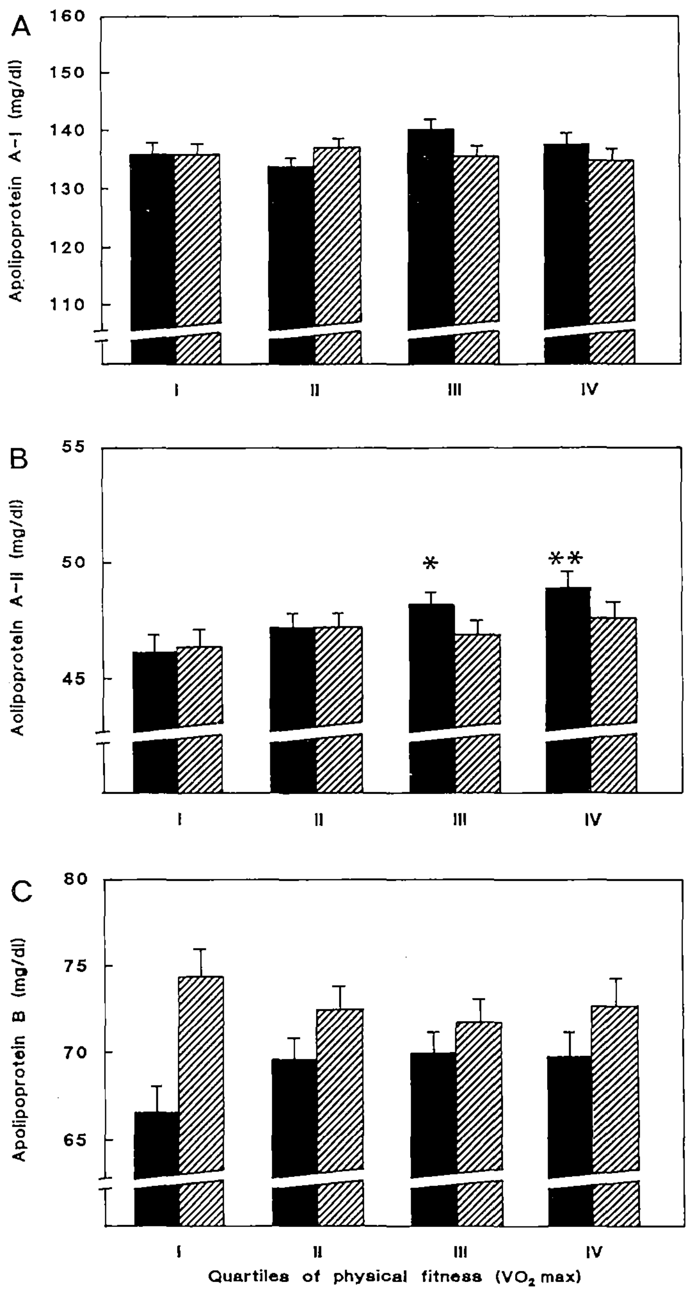

*Figure 5.1. Mean levels of serum apolipoproteins A-I, A-II and B with standard errors by quartile grouping of physical fitness. Adjustments were made for differences in age, skeletal age, height, weight and sum of four skinfolds. Category I refers to poor and IV to high physical fitness. The dark bars refer to boys and the arced bars to girls. * p = 0.02 vs I; ** p = 0.01 vs I.*

and anthropometric variables.

Table 5.5 shows the differences in serum lipid and lipoprotein levels between boys and girls with a VO_2max at or above the upper decile and below the 90th centile. In boys with a relatively high level of physical fitness total HDL cholesterol levels were higher. Lower LDL cholesterol levels were observed in girls with a relatively high VO_2max. For apolipoproteins no differences could be observed.

The HDL/total cholesterol ratio, HDL/LDL cholesterol ratio and apolipoprotein B/apolipoprotein A-I ratio were not associated with physical fitness.

Discussion

The main conclusion from this study is that there appears to be no association between serum lipids and lipoproteins, and physical fitness in schoolchildren aged 7 to 11 years. Also, no relation between apolipoprotein A-I or apolipoprotein B and maximal aerobic capacity could be found. Only in boys apolipoprotein A-II showed an increase with an increasing physical fitness. Boys and girls with relatively high levels of physical fitness showed respectively higher HDL cholesterol and lower LDL cholesterol levels.

The results presented here are based on a large study population of randomly selected schoolchildren and there is no reason to consider selective non-response. Although blood was sampled during the whole day and obtained from non-fasting subjects, this seemed not to have had a large influence on the levels of serum lipids and lipoproteins. Our observations on mean values and standard deviations of serum lipids and lipoproteins largely confirm previous reports on serum lipids in this age category, taking differences in methods of determination into account (26-31). Some of the children studied may be pubescent, which could result in declines of total cholesterol and several of the measured lipoproteins in the older age groups (26,29). However, no differences in mean levels and standard deviations of serum lipids and lipoproteins between four age categories, ranging from 7 to 11 years, could be found. This suggests that most of the children were probably pre-pubescent. Values of maximal oxygen uptake were within the ranges of data reported by Saris who used the same exercise protocol (32), although boys in the present study had lower values. The explanation of this difference might be the small sample size and the exclusion of those subjects that did not reach a respiratory quotient of 1.1 in the study of Saris. Physical fitness in the present study was assessed as accurately as possible. A maximal treadmill-protocol was applied and maximal oxygen uptake was measured directly. Generally accepted criteria were used to determine whether the respondent had achieved a

Table 5.3. Coefficients of linear regression (in (mg/dl)/(l/min)) with 95% confidence limits (CL) of serum lipids and lipoproteins on physical fitness in boys. Adjustments were made both for age alone (β_1) and for age, skeletal age, height, weight and sum of four skinfolds (β_2).

		Boys			
		β_1	*(95% CL)*	β_2	*(95% CL)*
Total cholesterol	(mg/dl)	-8.1	(-19.0, 2.8)	1.6	(-13.0, 16.1)
LDL cholesterol	(mg/dl)	-7.9	(-19.5, 3.7)	-0.6	(-16.2, 14.9)
HDL cholesterol	(mg/dl)	-0.7	(-5.1, 3.7)	-0.8	(-6.7, 5.1)
HDL_2 cholesterol	(mg/dl)	-1.2	(-4.7, 2.2)	-1.9	(-6.5, 2.7)
HDL_3 cholesterol	(mg/dl)	-0.7	(-3.4, 2.1)	-0.3	(-4.0, 3.3)
Apolipoprotein A-I	(mg/dl)	3.3	(-4.1, 10.7)	8.8	(-1.0, 18.6)
Apolipoprotein A-II	(mg/dl)	0.7	(-2.1, 3.6)	5.9	(2.2, 9.5)
Apolipoprotein B	(mg/dl)	-0.3	(-6.3, 5.7)	5.6	(-2.3, 13.4)

Table 5.4. Coefficients of linear regression (in (mg/dl)/(l/min)) with 95% confidence limits (CL) of serum lipids and lipoproteins on physical fitness in girls. Adjustments were made both for age alone (β_1) and for age, skeletal age, height, weight and sum of four skinfolds (β_2).

		Girls			
		β_1	*(95% CL)*	β_2	*(95% CL)*
Total cholesterol	(mg/dl)	-1.5	(-13.8, 10.8)	-5.9	(-23.7, 11.9)
LDL cholesterol	(mg/dl)	0.8	(-12.3, 14.0)	-1.7	(-20.4, 17.0)
HDL cholesterol	(mg/dl)	-3.3	(-7.8, 1.1)	-3.9	(-10.3, 2.4)
HDL_2 cholesterol	(mg/dl)	-1.8	(-5.2, 1.6)	-1.7	(-6.4, 3.1)
HDL_3 cholesterol	(mg/dl)	-2.2	(-4.6, 0.1)	-2.7	(-6.2, 0.8)
Apolipoprotein A-I	(mg/dl)	-6.6	(-14.2, 1.1)	-6.2	(-17.1, 4.7)
Apolipoprotein A-II	(mg/dl)	-0.9	(-3.8, 1.9)	2.6	(-1.5, 6.6)
Apolipoprotein B	(mg/dl)	1.6	(-5.3, 8.4)	-1.0	(-8.5, 8.5)

maximal exercise level (33). The best method for maximal exercise testing in children below 10 years is a treadmill test (34). The Bruce workload protocol provides variation in speed so that even young children are able to perform the test without difficulty and reproducibility of the results of this protocol among children is high (35,36).

Comparing studies on the association between physical activity and CVD risk indicators is rather difficult due to selection of relatively high or low physically active

Table 5.5. Mean differences (δ with 95% confidence limits (CL) in mg/dl) in serum lipid and lipoprotein levels between boys and girls with a maximal oxygen consumption at or above the upper decile and below the 90th centile of VO_2max (reference category). Adjustments were made for age, skeletal age, height, weight and sum of four skinfolds.

	Boys		*Girls*	
	δ	*(95% CL)*	δ	*(95% CL)*
Total cholesterol (mg/dl)	0.03	(-8.20, 8.26)	-8.82	(-17.93, 0.29)
LDL cholesterol (mg/dl)	0.26	(-8.60, 9.12)	-9.71	(-19.26, -0.16)
HDL cholesterol (mg/dl)	2.74	(0.61, 6.09)	-2.84	(-5.98, 0.30)
HDL_2 cholesterol (mg/dl)	1.70	(-0.81, 4.21)	-1.87	(-4.28, 0.54)
HDL_3 cholesterol (mg/dl)	1.10	(-0.86, 3.06)	-0.98	(-2.76, 0.80)

study populations, inadequate classification of the level of physical fitness, differences in measurement methods of serum lipids and lipoproteins, and differences in adjustment for potential confounders (37). Nonetheless, results from observational studies in adults mainly show higher levels of HDL, its subfraction HDL_2 cholesterol and the apolipoprotein A-I, serving as the major part of HDL_2 protein, in men and women with a higher physical fitness (38). No differences in levels of apolipoprotein A-II have been reported (39). When the endurance capacity of the subjects is extremely heterogenous, significant inverse associations are reported between physical fitness and total - and LDL cholesterol (40).

This study on children confirms previous results indicating no linear relation between physical fitness, either measured indirectly in a submaximal protocol or directly and with a maximal protocol, and serum lipids in comparable age categories (14,15,41). Boys and girls participating in this study with a relatively high level of physical fitness showed respectively higher HDL and lower LDL levels. However, this relation could not be confirmed by analysis in smaller subgroups comparing children with a physical fitness below the lower and above the upper decile. Reports of an association between levels of lipids and lipoproteins, including apolipoproteins A and B, with physical fitness in general concern older age groups as study population, starting at the onset of puberty (11,12,16,42). This phenomenon could be due to several mechanisms. If until puberty genetic factors rather than environmental factors determine serum lipids and lipoproteins in children (26), this could explain the findings of our study. On the other hand, physical activity may induce beneficial changes on CVD risk indicators, and improvement of physical fitness could be the intermediate factor (43). Then, due to a natural need for movement at a younger age a relatively large amount of physical activity is necessary to improve physical fitness. This could explain the positive results found in children with a relatively high level of physical fitness and the results found in older age groups. In previous studies no improvement of maximal aerobic capacity was found in children, aged 4 to 12 year, who received endurance training (44,45). These results were in contrast to other studies concerning adolescents and adults in whom clearly improvements of maximal aerobic capacity were achieved by endurance training (7-10,46,47). Yet, another explanation could be that physical fitness at a young age is mainly genetically determined, so that physical fitness is partly independent of the amount of daily physical activity (48-50). This could be reflected in the positive association found in several studies (15,51,52) between daily physical activity and lipid and lipoprotein levels in young children.

In summary, these observations suggest that there are no major associations between physical fitness and levels of lipids and lipoproteins in pre-pubertal children. It, therefore, appears unlikely that increasing physical fitness in young children would have a major favorable effect on their lipid profile.

Acknowledgement

This work was supported by a grant from the Netherlands Prevention Fund. The authors acknowledge Anneke van der Muil-Houwing, Ria Rijneveldshoek, Wilma Verbruggen, Frans Dullemeijer, Theo van der Berg and the students of the Faculty of Human Movement Sciences, University of Amsterdam (director prof. H.C.G. Kemper) for their work at the research center; Ton de Bruyn, Jeannette Drop, and René Vermeeren for their contribution in determining serum lipids and lipoproteins; and Yolanda Bekker-Wilthagen and Dick Tensen for their assistance in data-collection and -analysis.

References

1. Castelli WP, Garrison RJ, Wilson PWF, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham study. JAMA 1986;256:2835-8.
2. The Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events. J Chron Dis 1978;31:225-306.
3. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356222 primary screenees of the Multiple Risk Factor Intervention trial. JAMA 1986;256:2823-8.
4. Wallace RB, Anderson RA. Blood lipids, lipid-related measures, and the risk of atherosclerotic cardiovascular disease. Epidemiol Rev 1987;9:95-119.

5. Newman WP, Freedman DS, Voors AW, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. N Eng J Med 1986;314:138-44.
6. Tanaka K, Masuda J, Imamura T, et al. A nation-wide study of atherosclerosis in infants, children and young adults in Japan. Atherosclerosis 1988;72:143-56.
7. Huttunen JK, Länsimies E, Voutilainen E, et al. Effect of moderate physical exercise on serum lipoproteins. A controlled clinical trial with special reference to serum high-density lipoproteins. Circulation 1979;60:1220-9.
8. Hardman AE, Hudson A, Jones PRM, et al. Brisk walking and plasma high density lipoprotein cholesterol concentrations in previously sedentary women. Br Med J 1989;299:1204-5.
9. Kiens B, Jörgensen I, Lewis S, et al. Increased plasma HDL-cholesterol and apo A-I in sedentary middle-aged men after physical conditioning. Eur J Clin Invest 1980;10:203-9.
10. Thompson PD, Cullinane EM, Sady SP, et al. Modest changes in high-density lipoprotein concentration and metabolism with prolonged exercise training. Circulation 1988;78:25-34.
11. Tell GS, Vellar OD. Physical fitness, physical activity, and cardiovascular disease risk factors in adolescents: The Oslo youth study. Prev Med 1988;17:12-24.
12. Välimäki I, Hursti ML, Pihlakoski L, Viikari J. Exercise performance and serum lipds in relation to physical activity in schoolchildren. Int J Sports Med 1980;1:132-6.
13. Hofman A, Walter HJ. The association between physical fitness and cardivascular disease risk factors in children in a five-year follow-up study. Int J Epidemiol 1989;18:830-5.
14. Sady SP, Berg K, Beal D, et al. Aerobic fitness and serum high-density lipoprotein cholesterol in young children. Hum Biol 1984;56:771-81.
15. Sallis JF, Patterson TL, Buono MJ, Nader PR. Relation of cardiovascular fitness and physical activity to cardiovascular disease risk factors in children and adults. Am J Epidemiol 1988;127:933-41.
16. Rönnemaa T, Lehtonen A, Järveläinen H, et al. Plasma lipids and lipoproteins of young male athletes and the effect of their serum on cultured human aortic smooth muscle cells. Scand J Sports 1980;2:33-8.
17. Durnin JVGA, Rahaman MM. The assessment of the amount of fat in the human body from measurements of skinfold thickness. Br J Nutrition 1967;21:681-9.
18. Van Gent CM, Van der Voort HA, De Bruyn AM, Klein F. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-51.
19. Burstein M, Scholnick HR, Morfin R. Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. J Lipid Res 1970;11:583-95.
20. Grove TH. Effect of reagent pH on determination of high-density lipoprotein cholesterol by precipitation with sodium phosphotungstate-magnesium. Clin Chem 1979;25:560-4.
21. Gidez LI, Miller GJ, Burstein M, Sagle S, Eder HA. Separation and quantification of subclasses of human plasma high density lipoproteins by a simple precipitation procedure. J Lipid Res 1982;23:1206-23.
22. Cheung MC, Albers JJ. The measurement of apolipoprotein A-I and A-II levels in men and women by immunoassay. J Clin Invest 1977;60:43-50.

23. Tanner JM, Whitehouse RH, Marshall WA, Healy MJR, Goldstein H. Assessment of skeletal maturity and prediction of adult height (TW2 method). New York: Academic, 1975.
24. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973;85:546-62.
25. Åstrand PO. Experimental studies of physical working capacity in relation to sex and age. Copenhagen: Munksgaard, 1952.
26. Stiphout van WAHJ, Hofman A, Bruijn de AM, Valkenburg HA. Distributions and determinants of total and high-density lipoprotein cholesterol in Dutch children and young adults. Prev Med 1985;14:169-80.
27. Berenson GS, Srinivasan SR, Cresanta JL, et al. Dynamic changes of serum lipoproteins in children during adolescence and sexual maturation. Am J Epidemiol 1981;113:157-70.
28. Tamir I, Heiss G, Glueck CJ, Christensen B, Kwiterovich P, Rifkind BM. Lipid and lipoprotein distributions in white children ages 6-19 yr. The lipid research clinics program prevalence study. J Chron Dis 1981;34:27-39.
29. Viikari J, Åkerblom HK, Nikkari T, et al. Atherosclerosis precursors in Finnish children and adolescents. IV. Serum lipids in newborns, children and adolescents. Acta Paediatr Scand 1985;suppl 318:103-9.
30. Srinivasan SR, Freedman DS, Sharma C, Webber LS, Berenson GS. Serum apolipoproteins A-I and B in 2,854 children from a biracial community: Bogalusa Heart Study. Pediatrics 1986;78:189-200.
31. Solakivi-Jaakkola T, Nikkari T, Viikari J, et al. Atherosclerosis precursors in Finnish children and adolescents. VI. Serum apolipoproteins A-I and B. Acta Paediatr Scand 1985;suppl 318:119-25.
32. Saris WHM. Reference values for aerobic power of healthy 4- to 18-year-old Dutch children: preliminary results. In: Binkhorst RA, Kemper HCG, Saris WHM, eds. Children and exercise XI. Champaign: Human Kinetics Books, 1985:151-60.
33. Bar-Or O. Procedures for exercise testing in children. In: Katz M, Stiehm ER, eds. Pediatric sports medicine for the practitioner. New York: Springer-Verlag, 1983:315-41.
34. WHO. Exercise tests in relation to cardiovascular function. Geneva: Technical Report Series, 1968;338.
35. Cumming GR, Everatt D, Hastman L. Bruce treadmill test in children: normal values in a clinic population. Am J Cardiol 1978;41:69-75.
36. Saris WHM. Aerobic power and daily physical activity in children. With special reference to methods and cardiovascular risk indicators. Thesis. Nijmegen: Krips Repro Meppel, 1982.
37. Taylor HL. Physical activity: Is it still a risk factor? Prev Med 1983;12:20-4.
38. Haskell WL. Exercise-induced changes in plasma lipids and lipoproteins. Prev Med 1984;13:23-36.
39. Krauss RM, Lindgren FT, Wood PD, et al. Differential increases in plasma high density lipoprotein subfractions and apolipoprotein subfractions and apolipoproteins (APO-LP) in runners. Circulation 1977;56:4.
40. Cooper KH, Pollock ML, Martin RP, et al. Physical fitness levels vs. selected coronary

risk factors. JAMA 1976;236:166-9.
41. Saris WHM, Binkhorst RA, Cramwinckel AB, Waesberghe van F, Veen-Hezemans van der AM. The relationship between working performance, daily physical activity, fatness, blood lipids, and nutrition in schoolchildren. In: Berg K, Eriksson BO, eds. Children and exercise IX. Baltimore: University Park Press, 1980:166-74.
42. Nizankowska-Blaz T, Abramowicz T. Effects of intensive physical training on serum lipids and lipoproteins. Acta Paediatr Scand 1983;72:357-9.
43. Haskell WL. Physical activity and health: Need to define the required stimulus. Am J Cardiol 1985;55:4D-9D.
44. Gilliam TB, Freedom PS. Effects of a 12-week school physical fitness program on peak VO_2, body composition and blood lipids in 7- to 9-year-old children. Int J Sports Med 1980;1:73-8.
45. Yoshida T, Ishiko I, Muraoka I. Effect of endurance training on cardio-respiratory functions of 5 year old children. Int J Sports Med 1980;1:91-4.
46. Watson AWS. Three year study of the effects of exercise on active young men. Eur J Appl Physiol 1979;40:107-15.
47. Hagberg JM, Goldring D, Ehsani AA, et al. Effect of exercise training on the blood pressure and hemodynamic features of hypertensive adolescents. Am J Cardiol 1983;52:763-8.
48. Klissouras V. Heritability of adaptive variation. J Appl Physiol 1977;31:338-44.
49. Lorie G, Bouchard C, Leblanc C, et al. Familial similarity in aerobic power. Hum Biol 1982;54:801-12.
50. Weber G, Kartodihardjo W, Klissouras V. Growth and physical training with reference to heredity. J Appl Physiol 1976;40:211-15.
51. Thorland WG, Gilliam TB. Comparison of serum lipids between habitually high and low active pre-adolescent males. Med Sci Sports Exercise 1981;13:316-21.
52. Yamamoto A, Horibe H, Sawada S, et al. Serum lipid levels in elementary and junior high school children and their relationship to relative weight. Prev Med 1988;17:93-108.

CHAPTER 6

NON-PHARMACOLOGICAL INTERVENTION ON CARDIOVASCULAR RISK FACTORS IN CHILDREN

6.1 INTRODUCTION

It seems paradoxical that in our era of a boom in physical fitness and health consciousness, children are less fit as they were in past decades (1). In addition, results from several studies indicate that children become more obese (2) and obesity acquired in childhood tends to track into adult life (3).

Data from the Muscatine study reconfirmed the relation between body weight, relative weight and triceps skinfold thickness to blood pressure level in children (4). The relation between obesity and blood pressure has been firmly established in adults (5). In both adults and children associations were observed between indicators of relative overweight and total cholesterol, triglycerides, and low and very low density lipoprotein cholesterol (6-8).

These reports provided the rationale to study overweight children with regard to their cardiovascular risk factors. The studies presented in this chapter concern an intervention trial in children who had been overweight for several years. These children tend to have a relatively high risk of developing high blood pressure and an unfavorable lipid profile. Because intervention at a young age is to a great extent limited to non-pharmacological means, the effect of body weight reduction by caloric restriction and an increase of physical exercise was studied.

References

1. Strong WB. Physical activity and children. Circulation 1990;81:1697-701.
2. Stark O, Atkins E, Wolff OH, Douglas JWB. Longitudinal study of obesity in the National Survey of Health and Development. Br Med J 1981;283:13-7.
3. Garn SM, LaVelle M. Two-decade follow-up of fatness in early childhood. Am J Diseas Child 1985;139:181-5.
4. Lauer RM, Clarke WR, Beaglehole R. Level, trend, and variability of blood pressure during childhood: the Muscatine study. Circulation 1984;69:242-9.
5. Burton BT, Foster WR, Hirsch J, Van Itallie TB. Health implications of obesity: an NIH consensus development conference. Int J Obes 1985;9:155-69.
6. Khoury P, Morrison JA, Kelly K, Mellies M, Horvitz R, Glueck CJ. Clustering and interrelationships of coronary heart disease risk factors in schoolchildren, ages 6-19. Am J Epidemiol 1980;112:524-38.
7. Laskarzewski P, Morrison JA, Mellies MJ, et al. Relationships of measurements of body mass to plasma lipoproteins in schoolchildren and adults. Am J Epidemiol

1980;111:395-406.
8. Yamamoto A, Horibe H, Sawada S, et al. Serum lipid levels in elementary and junior high school children and their relationship to relative weight. Prev Med 1988;17:93-108.

6.2 EFFECT OF WEIGHT LOSS AND EXERCISE ON BLOOD PRESSURE: A RANDOMIZED TRIAL IN OVERWEIGHT CHILDREN

Introduction

Overweight is a serious health problem in Westernized societies (1). A high caloric intake evidently contributes to the occurrence of obesity, and a low level of physical activity has also been suggested to be an important factor (2,3). Overweight is increasingly common not only in adults but in children and adolescents as well. When overweight is present at a young age the chance of remaining obese as an adult is high (4-6). Overweight has repeatedly been associated with cardiovascular risk factors, such as blood pressure, serum lipids and diabetes mellitus (7,8) and has been found to be a major determinant of an excessive increase of blood pressure over time in childhood (9). Prevention and treatment of overweight at a young age may therefore be important, if it were only because of the difficulties to successfully reduce body weight in adults (10).

We conducted a randomized trial to examine the effects on blood pressure of weight reduction and increase in exercise in 105 overweight children.

Subjects and Methods

Population

From 1987 to 1989 1,558 children participated in a study on cardiovascular risk factors and physical fitness in childhood (11,12). Of those initially examined, 216 children in the upper 25% of the distribution of body weight, adjusted for age and height, were selected for a follow-up study together with a control group of 450 children randomly drawn from the same population. Eventually, 589 children participated in this follow-up study. Children were selected for the intervention study if they had a body weight above the 75th centile of the age and height specific body weight distribution during two consecutive examinations. Of the 174 children eligible, 105 youngsters (58 girls) aged 9 to 13 years agreed to participate in the present study.

Study Design

The children participating in the trial were randomly assigned to one of the three study groups, after stratification for sex and body weight. One group served as control group. The other two groups received either a total calorie reduced diet, or an exercise program for a period of twelve weeks. All participants entered the trial within two weeks. Blood pressure, anthropometric characteristics, physical fitness and dietary variables were measured at baseline, and after 6 and 12 weeks of intervention. 24 hour urine specimens were collected at 6 week intervals. Fasting venous blood samples were obtained and echocardiographic characteristics were measured at baseline and after 12 weeks.

Intervention and compliance

Weight reduction. At the start of the study two trained dieticians cross-checked the semiquantitative food frequency questionnaire, filled in by the parents at home and referring to the past month. Total caloric intake per day was estimated for each of the participants. Individual advice, aiming at a maximal intake of 1,250 kcal per day for 8 to 10 years old and 1,450 kcal per day for children aged 10-12 years, was given at home-visits once a week by the study dieticians. The parents played important roles in the intervention. Household cooking methods were evaluated and advice was given on the use of low caloric products. In addition, the children participated once a week in group sessions as part of a health education program (13). This program is based on the so-called 'traffic light diet' which categorizes foods according to eight nutritional groupings into red, yellow or green foods, according to caloric density (14,15). In these sessions aspects of overweight and attendance to the weight reduction were discussed in a playful way. Adherence to the weight reduction program was evaluated at home-visits by the dieticians and monitored by weighing the children weekly. Non-compliance was defined as a gain in weight of more than 1 kg after 12 weeks of intervention. This criterium was met by 3 children.

Exercise. In order to increase their aerobic capacity, the children assigned to the exercise group participated in a training program of two hours each week. The training comprised 50 minutes of aerobic exercise (mainly running games) after 10 minutes of warming-up, and the session ended with a 5-10 minutes cool-down period. The children were encouraged to exercise vigorously enough to reach heart rates equivalent to 70 to 80% of their maximal heart rate. The duration of the continuous exercise program was gradually increased until after 6 weeks most of the children were jogging continuously for 40 to 50 minutes. Compliance was assessed by monitoring frequencies of attendance and by continuous measurement of the heart rate during the training sessions using a sporttester PE3000 (16) to determine the exercise intensity. Compliance was defined as a total participation of 12 consecutive hours of training during the last 8 weeks of the intervention period and 3 children did not fulfill this criterium.

Measurements

Body weight and height were measured by weighing the children in their underwear, without shoes. Skinfold thickness was measured with a Holtain caliper at four sites: triceps, biceps, subscapular and suprailiac. Blood pressure was determined on the right arm with a Dinamap 845 XT device (17,18). At each occasion two readings were made, separated by a count of the pulse rate, with the subject in sitting position. The mean of these readings was used in the analysis. Diastolic blood pressure was defined as Korotkoff phase V.

Echocardiographic measurements were carried out using two-dimensional and M-mode echocardiography in supine left lateral position during six consecutive cardiac cycles. Cardiac dimensions, including end-diastolic intraventricular septum thickness (IVS), posterior left ventricular wall thickness (LVPW), and end-systolic posterior left ventricular wall thickness (LVPW-S), were obtained directly from the M-mode echocardiogram. Left ventricular mass (LVM) was calculated according to the formula $[(LVED+IVS+LVPW)^3 - LVED^3]x1.05$ (19). The average heart rate was estimated from six cardiac cycles.

Subjects were asked to abstain from caffeine-containing beverages and intensive exercise 24 hours before blood sampling. Blood was collected from 12 hours fasting subjects, using an intravenous cannula after 20 minutes of quiet recumbency. Plasma from immediately chilled heparinized blood, containing 6 mg reduced gluthatione, was rapidly frozen at -80°C and analyzed for catecholamines in a blinded fashion, using high-performance liquid chromatography with fluorimetric detection (20). In 44 children no blood samples were obtained due to refusal or failure to draw blood according to the standardized protocol. They were equally distributed over the three groups, and changes in weight or physical fitness in these children did not differ from the other participants. Average urinary electrolyte and catecholamine excretion was estimated from one 24-hour specimen.

Questionnaires on daily food consumption were completed covering the three measurement periods. From these, total caloric and total fat intake among other variables were calculated using a computerized food composition table (21).

Finally, maximal oxygen consumption (VO_2max) was measured during a Bruce treadmill test (22-24). Heart rate was calculated from a continuous ECG recording. Criteria for reaching maximal exercise were leveling off of oxygen uptake (i.e., no increase or less than 2 ml/kgmin) and/or leveling off of the heart rate despite an increased workload. An additional, secondary, criterium was a maximal respiratory gas exchange ratio greater than 1.0. All children participating in the study succeeded in reaching maximal exercise levels.

Data Analysis

The effect of the exercise and weight reduction intervention on blood pressure was analyzed in several ways. Firstly, the overall effect on blood pressure was examined by comparing mean levels between the intervention groups and the control group after 6 and 12 weeks. Secondly, the net change in blood pressure in the exercise and the weight reduction group was analyzed with the control group as reference, using a multiple linear regression model. One sided p values (p_1) and 90% confidence limits were used for the effects on blood pressure, and two sided p values (p_2) and 95% confidence limits for the other variables. Finally, subgroup analyses were performed according to predefined groups, potentially predictive of an intervention effect and categorized according to the median base-line urinary catecholamines and base-line body weight.

In the analyses three children were excluded because they did not complete the study. One, who was in the exercise group, withdrew immediately after the randomization. Two, who were in the control group, were not able to participate in the examination at the end of the intervention period due to influenza with high fever. The base-line characteristics of these three children were similar to those of the other participants.

Results

In Table 6.2.1 base-line characteristics of the study subjects are presented. The data show that after randomization all characteristics of the participants were well balanced across the three study groups.

A mean growth of 2 kg in body weight was observed in the exercise and the control group after 12 weeks of intervention (Table 6.2.2). Body weight did not increase in the weight reduction group ($p_2<0.01$). Height increased to the same extent in all three study groups with an average 1.8 cm. A decrease in the sum of four skinfolds was observed in the weight reduction group but not in the other groups. When maximal aerobic capacity was expressed per kg body weight, a small but statistically nonsignificant increase for the exercise group was observed. No changes were observed in echocardiographic parameters and plasma catecholamines. Mean urinary adrenaline excretion in the weight reduction group was lower than in the control group after intervention ($p_2=0.02$). The urinary excretion of electrolytes

Table 6.2.1. Base-line characteristics* in the three study groups.

	Exercise *n = 34*		*Control* *n = 33*		*Weight reduction* *n = 35*	
Sex (M/F)	14/20		15/18		15/20	
Age (yrs)	10.4	(0.8)	10.3	(0.8)	10.5	(0.8)
Body weight (kg)	41.2	(6.9)	42.4	(7.7)	42.5	(6.6)
Height (cm)	147.6	(9.1)	147.2	(8.6)	148.7	(8.4)
Sum of skinfolds (mm)	48	(17)	56	(22)	52	(23)
Systolic blood pressure (mmHg)	112	(8)	110	(8)	109	(8)
Diastolic blood pressure (mmHg)	64	(6)	65	(7)	62	(8)
Heart rate in rest (beats/min)	85	(13)	84	(9)	80	(12)
VO_2max (l/min)	1.80	(0.30)	1.78	(0.32)	1.81	(0.28)
VO_2max/kg (ml/min)/kg	43.8	(5.5)	42.2	(5.7)	43.1	(7.0)
Left ventricular mass (g)	114	(20)	118	(20)	119	(18)
Intraventricular septum (mm)	7.1	(0.7)	7.2	(0.7)	7.3	(0.7)
Posterior left ventricular wall (mm)	7.2	(0.6)	7.3	(0.6)	7.3	(0.5)
End-systolic posterior left ventricular wall (mm)	12.0	(1.0)	11.9	(0.9)	12.0	(0.9)
Urinary noradrenaline (μg/24h)	19	(8)	21	(9)	22	(10)
Urinary adrenaline (μg/24h)	4.0	(2.6)	4.2	(2.6)	4.2	(2.2)
Urinary dopamine (μg/24h)	186	(81)	221	(78)	222	(89)
Urinary sodium (mmol/24h)	93	(38)	103	(42)	89	(29)
Urinary potassium (mmol/24h)	52	(17)	52	(18)	52	(21)
Urinary creatinine (g/24h)	8.01	(1.9)	8.0	(1.9)	8.4	(1.9)
Total caloric intake (kcal/day)	2141	(362)	2155	(453)	2037	(525)
Total fat (g/day)	89	(22)	92	(26)	91	(40)

* Values are means with standard deviations in parentheses

remained stable during the study in all groups. Total calorie intake and energy adjusted total fat intake was lower in children allocated to the weight reduction intervention, compared to their controls. Intake of all other nutrients remained equal during the intervention. No change in calorie or nutrient intake was observed in children in the exercise group.

Table 6.2.2. Anthropometric characteristics, physical fitness, echocardiographic characteristics, biochemical and dietary variables+ after 12 weeks of intervention.

	Exercise *n = 34*	*Control* *n = 33*	*Weight reduction* *n = 35*
Body weight (kg)	43.2 (1.3)	44.4 (1.4)	42.2 (1.1)*
Height (cm)	149.6 (1.6)	149.0 (1.5)	150.3 (1.4)
Sum of skinfolds (mm)	49 (3)	55 (4)	44 (3)*
Heart rate in rest (beats/min)	81 (2)	82 (2)	79 (2)
VO_2max (l/min)	1.89 (0.05)	1.86 (0.06)	1.85 (0.05)
VO_2max/kg (ml/min)/kg	44.1 (1.0)	41.9 (1.0)	44.3 (1.2)
Left ventricular mass (g)	122 (4)	126 (4)	122 (4)
Intraventricular septum (mm)	7.3 (0.1)	7.5 (0.1)	7.4 (0.1)
Posterior left ventricular wall (mm)	7.4 (0.1)	7.5 (0.1)	7.3 (0.1)
End-systolic posterior left ventricular wall (mm)	12.5 (0.1)	12.2 (0.2)	11.9 (0.2)
Urinary noradrenaline (μg/24h)	24 (1)	29 (2)	25 (3)
Urinary adrenaline (μg/24h)	4.3 (0.5)	5.6 (0.6)	4.3 (0.4)**
Urinary dopamine (μg/24h)	253 (14)	281 (18)	246 (16)
Urinary sodium (mmol/24h)	96 (8)	109 (9)	99 (6)
Urinary potassium (mmol/24h)	48 (3)	51 (3)	52 (3)
Urinary creatinine (g/24h)	8.0 (1.0)	7.8 (0.6)	8.3 (0.6)
Total caloric intake (kcal/day)	2141 (114)	2224 (87)	1662 (46)*
Total fat (g/kcal)	0.042 (0.001)	0.042 (0.001)	0.040 (0.001)#

+ Values are means with standard errors in parentheses
* p values are given for differences from base-line, with control group as reference;
* $p < 0.01$; ** $p = 0.02$; # $p = 0.03$

In Figure 6.2.1 mean levels of blood pressure with standard errors are presented at base-line and at 6 and 12 weeks of intervention. After 12 weeks of intervention mean systolic blood pressure level was 106 mmHg (SE 1.4) in the weight reduction group, 109 mmHg (SE 1.4) in the exercise group and 110 mmHg (SE 1.6) in the controls. Mean systolic blood pressure was lower in the diet group compared to the controls (p_1=0.02). No difference in mean systolic blood pressure level was observed between the exercise group and controls. For diastolic blood pressure a decrease was

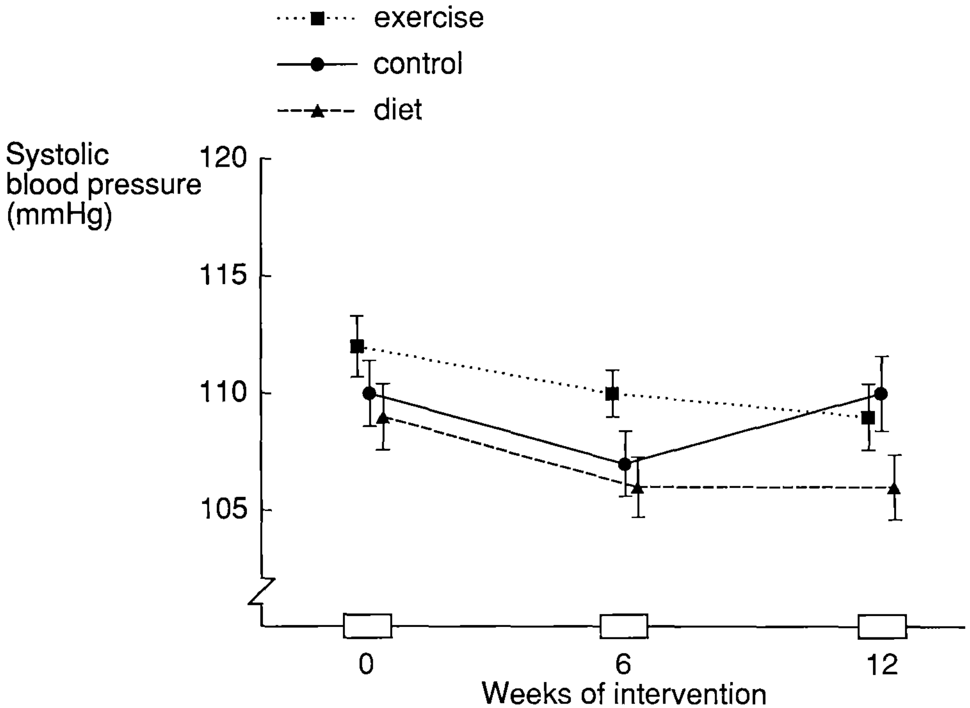

Figure 6.2.1. *Blood pressure levels at base-line and after 6 and 12 weeks of intervention. Values are means with standard errors.*

found in all three study groups after 12 weeks. No difference in diastolic blood pressure level was found between the three study groups after 12 weeks.

Net changes in blood pressure are presented for the study group as a whole in Table 6.2.3. The control group served as reference. No effect could be found on diastolic blood pressure, neither in the exercise group nor in the weight reduction group. After 12 weeks systolic blood pressure was 3.1 mmHg lower in the exercise group (90% confidence limits: -6.2, 0.1; p_1= 0.06) and 3.3 mmHg lower in the weight reduction group (90% confidence limits: -6.4, -0.2; p_1=0.04), compared to the control group. When the analysis was restricted to the compliant group only, the mean fall in systolic blood pressure was 3.5 mmHg (90% confidence limits: -6.8, -0.3; p_1=0.04) and 3.6 mmHg (90% confidence limits: -6.7, -0.4; p_1=0.04) in the exercise and the weight reduction group, respectively, relative to the control group.

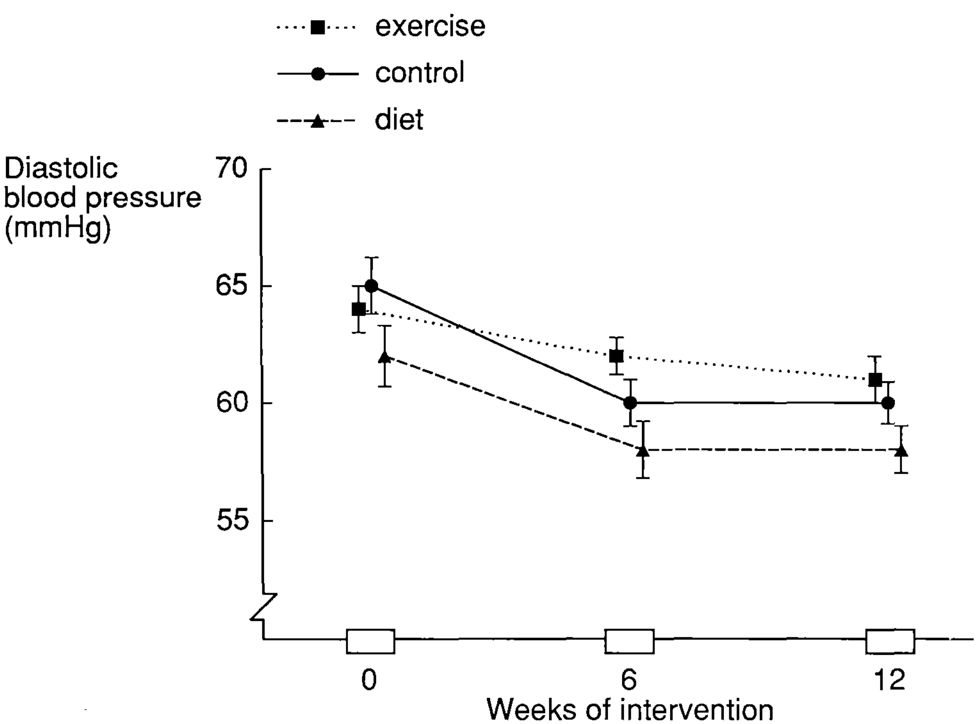

***Figure 6.2.1.** (cont.) Blood pressure levels at base-line and after 6 and 12 weeks of intervention. Values are means with standard errors.*

In Table 6.2.4 the average fall in blood pressure after 12 weeks of intervention is presented in exercise, weight reduction and control subjects with baseline urinary catecholamine excretion above and below the median. A fall in systolic blood pressure was observed for the exercise (5.9 mmHg; SE 2.7) and weight reduction group (3.5 mmHg; SE 1.1) in those children with urinary noradrenaline above the median, whereas no change was found for the control subjects. Also, for those subjects with a dopamine level above the median a decrease in systolic blood pressure was found in the exercise (7.1 mmHg; SE 2.4) and the weight reduction group (3.5 mmHg; SE 1.3), but no such effect was observed in the control group. Adrenaline excretion was not predictive of an effect of intervention on blood pressure. In addition, there appeared to be no difference in blood pressure fall based on the level of initial body weight, adjusted for differences in height and age.

Table 6.2.3. Net changes* in blood pressure after 6 and 12 weeks of intervention for the total group (n=102). The control group is used as reference group.

	6th week	*12th week*
Systolic blood pressure (mmHg)		
Exercise	1.8 (-1.3, 4.9)	-3.1 (-6.2, 0.1)
Weight reduction	0.5 (-2.5, 3.6)	-3.3 (-6.4, -0.2)
Diastolic blood pressure (mmHg)		
Exercise	1.8 (-0.8, 4.4)	1.1 (-1.3, 3.5)
Weight reduction	0.4 (-3.2, 3.3)	0.7 (-0.3, 1.8)

* Values are means with 90% confidence limits in parentheses

Table 6.2.4. Change+ in systolic (SBP) and diastolic (DBP) blood pressure after 12 weeks of intervention in exercise, weight reduction and control group subjects with baseline urinary catecholamine excretion above and below the median.

	Exercise	*Control*	*Weight reduction*
Noradrenaline $\geq$ P50			
Change SBP (mmHg)	-5.9 (2.7)*	0.0 (1.7)	-3.5 (1.1)*
Change DBP (mmHg)	-4.7 (1.8)*	-4.1 (1.3)*	-3.8 (1.3)*
Noradrenaline < P50			
Change SBP (mmHg)	-0.3 (1.8)	0.3 (1.7)	-2.8 (2.4)
Change DBP (mmHg)	-2.0 (1.3)	-4.8 (1.6)*	-3.6 (1.8)
Dopamine $\geq$ P50			
Change SBP (mmHg)	-7.1 (2.4)*	-0.1 (1.5)	-3.5 (1.3)*
Change DBP (mmHg)	-4.4 (1.3)*	-5.7 (1.2)*	-4.9 (1.3)*
Dopamine < P50			
Change SBP (mmHg)	0.3 (2.0)	0.4 (1.8)	-2.8 (2.1)
Change DBP (mmHg)	-2.4 (1.6)	-2.7 (1.7)	-2.7 (1.6)

+ Values are means with standard errors in parentheses

* $p < 0.05$

All analyses have been performed for boys and girls separately, without indicating any major differences according to gender.

Discussion

The main finding of this study is that in relatively overweight children a reduction in systolic blood pressure may be achieved by body weight reduction, and increased exercise. When the intervention effect was studied in predefined subgroups with contrasting urinary catecholamine excretion, the fall in systolic blood pressure appears to be most prominent, in particular in those children with initially higher levels of urinary noradrenaline and dopamine excretion.

Before these findings can be accepted, some methodological aspects of the study must be considered. As blinding of the participants for the intervention status could not be achieved, the study was not performed double-blind. However, all measurements were carried out by observers who were not informed about the intervention group of the participant. Furthermore, blood pressure was measured with an automatic device and laboratory analyses were blinded. In addition, the exact hypotheses studied were not disclosed to the children and their parents before the trial was completed.

Although participation and intensity of the training during the exercise intervention were closely monitored, using registration of heart frequency, a clear increase in maximal oxygen consumption could not be found. Several factors might explain this finding. It could be that a frequency of exercise training of two hours per week during 12 weeks is not sufficient to increase maximal aerobic capacity, although several previous studies with a similar program did report favorable changes in physical fitness (24,25). However, the children in our study may have been too young to increase their aerobic capacity on moderate exercise intervention (26,27). Another explanation could be that the change in physical fitness could not yet be determined by measuring aerobic capacity. We studied other characteristics of physical fitness, such as maximal heart rate, running time on the treadmill, and heart rate in rest. An increase in running time and a decrease in maximal heart rate and heart rate in rest was observed for the exercise group, the difference, however, not reaching statistical significance when compared to the control group.

Whatever mechanisms are involved, systolic blood pressure was lower after 12 weeks of exercise intervention compared to the control group. Similar to our findings Hagberg et al., who studied the effect of exercise training in hypertensive adolescents, reported a decrease in systolic and diastolic blood pressure after exercise training with an increase in maximal oxygen uptake and no concomittant changes in body weight (28). This could imply that, although physical fitness and body weight are closely related, the effect of an increase in physical fitness on blood pressure seems to be independent of body weight.

Studies on blood pressure and overweight have reported a strong association between these factors in childhood and adolescence (29-31). A decrease in blood pressure of approximately 10 mmHg was described by Rocchini et al. in extremely obese adolescents after a weight reduction program of 20 weeks which resulted in an mean fall in body weight of 7 kg compared to the controls (32). In our study, a moderate decrease of 2 kg in body weight, compared to the controls, was already accompanied with a fall in systolic blood pressure of 3 mmHg.

The mechanisms behind the changes in blood pressure in the intervention groups are still speculative. For the exercise intervention, concomittant changes in body weight, obesity, dietary factors or electrolytes with regard to blood pressure could potentially explain an effect on blood pressure. Yet, no significant changes in body weight, sum of four skinfolds, dietary intake or electrolyte excretion could be observed for this intervention group. Similarly, no changes in echocardiographic parameters occurred during the trial, although several previous studies have demonstrated that cardiac characteristics are strongly related to body weight at this age (33,34).

An association was observed between the initial level of urinary catecholamines, and the fall in systolic blood pressure in both intervention groups. This may imply that urinary catecholamine levels are predictive of the effect on blood pressure in overweight children and that children with high catecholamine excretion should be particularly eligible for intervention.

In summary, we have demonstrated that already at a young age systolic blood pressure reduction can be achieved after moderate and generally applicable means of intervention. Thus, body weight reduction and increase of exercise may be important in reducing the chance of developing a high blood pressure, and subsequently in achieving long-term reduction of the risk of cardiovascular disease.

Acknowledgement

We are deeply grateful to the children and their parents for their dedicated contribution during the trial. We would like to thank gratefully Mrs H. Mollee-Sijbrandy, who stimulated the children to participate with great enthousiasm in both the weight reduction and the exercise group. We acknowledge Mrs M. de Vette and Mrs M. van den Bergh for their specific contribution to the weight reduction group, Mrs A. van der Muil-Houwing, Mrs R.

Rijneveldshoek for their invaluable work at the research centre, Mrs H. van Meurs for skilful echocardiography, Mrs H. Kornman-van den Bosch for her fine laboratory assistance, Mrs G. Buitelaar, Mrs L. Deunk, Mrs B. Hutten, Mrs M. Veeger for performing excellently all maximal exercise tests, and finally Mr M. Eijgermans and Mrs Y. Bekker-Wilthagen for their assistance with data-analysis. This study was supported by General Biscuits, The Netherlands, and Riedel Drinks, Ede, The Netherlands.

References

1. Aristimuno GG, Foster TA, Voors AW, Srinivasan SR, Berenson GS. Influence of persistent obesity in children on cardiovascular risk factors: The Bogalusa heart study. Circulation 1984;69:895-904.
2. Dietz WH, Gortmaker SL. Do we fatten our children at the television set? Obesity and television viewing in children and adolescents. Pediatrics 1985;75:807-12.
3. Armstrong N, Balding J, Gentle P, Kirby B. Patterns of physical activity among 11 to 16 year old British children. Br Med J 1990;301:203-5.
4. Garn SM, LaVelle M. Two-decade follow-up of fatness in early childhood. Am J Diseas Child 1985;139:181-5.
5. Stark O, Atkins E, Wolff OH, Douglas JWB. Longitudinal study of obesity in the National Survey of Health and Development. Br Med J 1981;283:13-7.
6. Charney E, Goodman HC, Mcbride M, Lyon B, Pratt R. Childhood antecedents of adult obesity. Do chubby infants become obese adults? N Eng J Med 1976;295:6-9.
7. Berenson GS. Cardiovascular risk factors in children. The early natural history of atherosclerosis and essential hypertension. New York: Oxford University Press, 1980:274-89,330-49.
8. Burton BT, Foster WR, Hirsch J, Van Itallie TB. Health implications of obesity: an NIH consensus development conference. Int J Obes 1985;9:155-69.
9. Clarke WR, Woolson RF, Lauer RM. Changes in ponderosity and blood pressure in childhood: the Muscatine study. Am J Epidemiol 1986;124:195-206.
10. Council on Scientific Affairs. Treatment of obesity in adults. JAMA 1988;260:2547-51.
11. Man de SA, Grobbee DE, Stiphout van WAHJ, Valkenburg HA, Hofman A. Serum lipids, lipoproteins and physical fitness in childhood. Am J Epidemiol (in press).
12. Man de SA, Grobbee DE, Hofman A. A study on blood pressure and physical fitness in childhood in the Netherlands. J Hypertension 1989;7:430.
13. Houten van M. 'Door dik en dun.' A health education program for overweight children. Vlaardingen, 1981.
14. Epstein LH, Masek BJ, Marshall WR. A nutritionally based school program for control of eating in obese children. Behav Ther 1978;9:766-88.
15. Epstein LH, Wing RR, Koeske R, et al. Child and parent weight loss in family-based behavior modification programs. J Consult Clin Psychol 1981;49:674-85.
16. Léger L, Thivierge M. Heart rate monitors: validity, stability, and functionality. Phys Sportsmed 1988;16:50-7.
17. Colan SD, Fujii A, Borow K, MacPherson D, Sanders SP. Noninvasive determination

of systolic and diastolic blood pressure in neonates, infants, young children: comparison with central aortic pressure measurements. Am J Cardiol 1983;52:867-70.

18. Ellison RC, Gamble WJ, Taft DS. A device for the automatic measurements of blood pressure in epidemiologic studies. Am J Epidemiol 1984;120:542-9.
19. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. Circulation 1977;55:613-8.
20. Van der Hoorn FAJ, Boomsma F, Man in 't Veld AJ, Schalekamp MADH. Determination of catecholamines in human plasma by high-performance liquid chromatography: comparison between a new method with fluorescence detection and an established method with electrochemical detection. J Chromatography 1989:487:17-28.
21. Commissie N.C.V. Voorlichtingsbureau voor de voeding. N.E.V.O. tabel (Dutch computerised food composition table). 's Gravenhage: 1989.
22. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973;85:546-62.
23. Åstrand PO. Experimental studies of physical working capacity in relation to sex and age. Copenhagen: Munksgaard, 1952:103-24.
24. Bar-Or O. Procedures for exercise testing in children. In: Katz M, Stiehm ER, eds. Pediatric sports medicine for the practitioner. New York: Springer-Verlag, 1983:305-41.
25. Åstrand PO, Rodahl K. Textbook of work physiology. Physiological bases of exercise. New York: McGraw-Hill Book Company, 1986:354-91.
26. Gilliam TB, Freedom PS. Effects of a 12-week school physical fitness program on peak VO_2, body composition and blood lipids in 7- to 9-year-old children. Int J Sports Med 1980;1:73-8.
27. Klissouras V. Heritability of adaptive variation. J Appl Physiol 1977;31:338-44.
28. Hagberg JM, Goldring D, Ehsani AA et al. Effect of exercise training on the blood pressure and hemodynamic features of hypertensive adolescents. Am J Cardiol 1984;52:763-8.
29. Lauer RM, Connor WE, Leaverton PE, et al. Coronary heart disease risk factors in school children. The Muscatine study. J Pediatrics 1975;86:697-708.
30. Webber LS, Voors AW, Srinisivan SR, et al. Occurrence in children of multiple risk factors for coronary artery disease. The Bogalusa Heart study. Am J Epidemiol 1977;106:101-15.
31. Aristimuno GG, Foster TA, Voors AW, et al. Influence of persistent obesity in children on cardiovascular risk factors. The Bogalusa Heart study. Circulation 1984;69:895-904.
32. Rocchini AP, Katch V, Anderson J, Hinderliter J, Becque D, Martin M, Marks C. Blood pressure in obese adolescents: effect of weight loss. Pediatrics 1988;82:16-23.
33. McMahon SW, Wilcken EL, McDonald GJ. The effect of weight reduction on left ventricular mass: a randomized controlled trial in young, overweight hypertensive

patients. N Eng J Med 1986;314:334-9.
34. Burke GL, Arcilla RA, Culpepper WS, Webber LS, Chiang YK, Berenson GS. Blood pressure and echocardiographic measures in children: the Bogalusa heart study. Circulation 1987;75:106-14.

6.3 EFFECT OF EXERCISE AND WEIGHT REDUCTION ON PLASMA LIPIDS AND LIPOPROTEINS IN OVERWEIGHT CHILDREN

Introduction

An increasing number of children and adolescents is overweight (1). Even though not all overweight children will necessarily become overweight adults, the rising prevalence of obesity in children is likely to be reflected in increasing obesity in adult years (2-4). Both in adults and children unfavorable associations were observed between relative overweight and total cholesterol, triglycerides, and low and very low density lipoprotein cholesterol (5-12). Plasma lipids and lipoproteins are important and independent risk factors of the occurrence of cardiovascular disease (13-16). Early intervention on its risk factors may provide means of reducing the risk to develop cardiovascular disease later in life. In view of this, the present study was undertaken to examine the effects of weight reduction and increase in physical fitness on lipids and lipoproteins in overweight children, participating in a randomized controlled trial.

Methods

Population

From a group of 1,558 children participating in a study on cardiovascular risk factors and physical fitness in childhood during the time period 1987-1989 (17,18), a random sample was selected for a follow-up study in 1989. In addition, children were selected with a body weight in the upper quarter of the age and height adjusted distribution of body weight. From this cohort of 589 children, subjects were invited for the present intervention study, who had a body weight above the 75th centile of the weight distribution during both the initial study and the follow-up study. Of 174 children eligible, 105 youngsters (58 girls) aged 9 to 13 years agreed to participate in the present study, resulting in a response rate of 60,3%.

Design of the study

All participants were randomly assigned to one of the three study groups after stratification for sex and body weight. One group served as control group. The other children entered either an exercise program of two hours per week or a program aiming at a reduction of total caloric intake through dietary intervention. The intervention continued for a period of twelve weeks and all participants entered the trial within two weeks. Blood pressure, anthropometric characteristics, physical fitness and dietary variables were measured at baseline, and after 6 and 12 weeks of intervention. 24 hour urine specimens were collected at 6 week intervals. Fasting venous blood samples were obtained at baseline and after 12 weeks.

Intervention and compliance

Exercise. The children participated in an exercise program of two hours per week in order to enlarge their aerobic capacity. After 10 minutes of warming-up, the training consisted of 50 minutes of aerobic exercise (mainly running games), and the session ended with a 5 to 10 minutes cool-down period. The intensity of the training was equivalent to 70 to 80% of the maximal heart rate of each child, measured during a maximal exercise test. The duration of the continuous exercise program was gradually increased until after 6 weeks most of the children were jogging continuously for 40 to 50 minutes. Compliance was assessed by monitoring frequencies of attendance and measuring heart rate during the training with a sporttester PE3000 (19) to determine exercise intensity.

Weight reduction. Before the start of the study a semiquantitative food frequency questionnaire was filled in by the parents, concerning the past month. The questionnaire was cross-checked by two trained dieticians. For each participant an estimate was obtained of the amount of total calories consumed per day. As part of the weight reduction program individual advices, aiming at 1,250 Kcal per day for 8 to 10 years old and 1,450 Kcal per day for children aged 10-12 years, were given at weekly home-visits. The parents were closely involved in the intervention. House-hold cooking methods were evaluated and if necessary advices were given on the use of low caloric products. In addition, weekly group sessions were held in which aspects of overweight and adherence to the diet were discussed according to a health education program (20). This program was based on the so-called 'traffic light diet' which categorizes foods into a red, yellow or green group, according to caloric density (21,22). Adherence to the weight reduction program was evaluated at the home-visit by the dieticians and monitored by weighing the children weekly.

Measurements

Body weight and height were measured by weighing the children in their underwear without shoes. At four sites skinfold thickness (triceps, biceps, subscapular and suprailiac) was measured with a Holtain caliper.

Fasting blood samples were obtained and frozen as plasma at -20°C. All samples were analyzed blindly. Plasma total cholesterol was determined by an automated enzymatic procedure (23). After precipitation high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol were measured by the same method. The phosphotungstate method according to Burstein and coworkers (24), with a minor modification as described by Grove (25), was used for precipitation of HDL. HDL cholesterol subfractions, HDL_2 and HDL_3, were precipitated with Mn^{2+}-heparin and dextransulfate according to Gidez et al. (26). For LDL cholesterol, precipitation was carried out with polyvinyl sulphate. Apolipoproteins A-I and B were assayed by an automated immunoturbidimetric method (Kone Diagnostics Finland). Apolipoprotein A-II was determined by radial immunodiffusion against specific antiplasma according to Cheung and Albers, with slight modifications (27). Triglycerides were determined according to Giegel et al. (28). All determinations were carried out in our own laboratory, which participates in the Lipid Standardization Program of the World Health Organization's Regional Lipid Reference Center in Prague, Czechoslovakia.

Physical fitness was determined directly by measuring maximal oxygen consumption (VO_2max) (29-31). Maximal exercise levels were reached if leveling off of oxygen uptake (i.e., no increase or less than 2 ml/kgmin) and/or leveling off of the heart rate despite an increased workload occurred. An additional criterium was a maximal respiratory gas exchange ratio greater than 1.0. Heart rate was calculated from a continuous ECG recording. All children participating in the study succeeded in reaching maximal exercise levels.

Electrolyte excretion in urine was estimated from one 24-hour specimen.

Questionnaires on daily food consumption were completed covering the three measurement periods. A computerized food composition table was used to determine total caloric, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, the ratio of polyunsaturated and saturated fat (P/S ratio), cholesterol, linoleic acid, carbohydrates, mono-, di- and polysaccharides intake (32).

Data-analysis

The effects of the exercise and weight reduction intervention were analyzed in two ways. Mean levels of plasma lipids and lipoproteins were compared between the three study groups after 12 weeks of intervention. In an additional analysis, the results for the exercise and weight reduction group were expressed as net changes from baseline with the control group as reference in a multiple linear regression model. One sided p values (p_1) were calculated for the results on plasma lipids and lipoproteins. For the effect on the other variables two sided p values (p_2) were used.

In the analyses presented below three children are excluded because they did not complete the study. One, who was in the exercise group, withdrew immediately

Table 6.3.1. Base-line characteristics* in the three study groups.

	Exercise (*n* = 34)		*Control* (*n* = 33)		*Weight reduction* (*n* = 35)	
Sex (M/F)	14/20		15/18		15/20	
Age (yrs)	10.4	(0.8)	10.3	(0.8)	10.5	(0.8)
Body weight (kg)	41.2	(6.9)	42.4	(7.7)	42.5	(6.6)
Height (cm)	147.6	(9.1)	147.2	(8.6)	148.7	(8.4)
Sum of skinfolds (mm)	48	(17)	56	(22)	52	(23)
VO_2max (l/min)	1.80	(0.30)	1.78	(0.32)	1.81	(0.28)
VO_2max/kg (ml/minkg)	43.8	(5.5)	42.2	(5.7)	43.1	(7.0)
Total cholesterol (mg/dl)	177	(34)	192	(29)	183	(39)
LDL cholesterol (mg/dl)	104	(31)	117	(23)	106	(36)
Triglycerides (mg/dl)	77	(29)	86	(44)	81	(28)
HDL cholesterol (mg/dl)	50	(13)	51	(11)	51	(11)
HDL_2 cholesterol (mg/dl)	12	(9)	11	(7)	12	(9)
HDL_3 cholesterol (mg/dl)	38	(7)	41	(7)	40	(6)
Apolipoprotein A-I (mg/dl)	127	(18)	130	(15)	130	(17)
Apolipoprotein A-II (mg/dl)	46	(5)	47	(5)	48	(6)
Apolipoprotein B (mg/dl)	65	(17)	73	(16)	65	(14)

* Values are means with standard deviations in parentheses

after the randomization. Two, who were in the control group, were not able to participate in the measurement periods after 12 weeks at the end of the intervention period due to influenza with high fever. The base-line characteristics of these three children were similar to those of the other participants.

Results

Base-line characteristics of the study subjects on anthropometry, physical fitness, plasma lipids and lipoproteins are presented in Table 6.3.1. Data on dietary intake are given in Table 6.3.2. The Tables show that all characteristics of the study groups were quit well balanced after randomization, except for apolipoprotein B which appeared to be lower in the intervention subjects compared to the control subjects.

Table 6.3.2. Base-line nutrient intake* in the three study groups.

	Exercise (*n* = *34*)		*Control* (*n* = *33*)		*Weight reduction* (*n* = *35*)	
Total calorie intake (kcal/day)	2294	(388)	2309	(485)	2174	(544)
Total fat (g/day)	95	(23)	99	(28)	97	(43)
Saturated fat (g/day)	41	(11)	42	(12)	39	(9)
Monounsaturated fat (g/day)	36	(11)	36	(10)	36	(12)
Polyunsaturated fat (g/day)	16	(6)	19	(10)	21	(26)
P/S ratio	0.46	(0.18)	0.53	(0.23)	0.51	(0.31)
Cholesterol (mg/day)	252	(64)	266	(99)	248	(84)
Linoleic acid (g/day)	13	(6)	17	(9)	18	(26)
Carbohydrates (g/day)	163	(38)	159	(39)	140	(42)
Mono- and disaccharides (g/day)	121	(26)	121	(33)	114	(31)
Polysaccharides (g/day)	287	(50)	283	(57)	257	(63)

* Values are means with standard deviations in parentheses

In Table 6.3.3 mean values of body weight, height, sum of four skinfolds, physical fitness and diet, expressed per total caloric intake per day, are shown for each of the three groups separately. An increase of 2 kg in body weight was observed for the exercise and the control group, but not for the weight reduction group ($p_2<0.01$). Height increased during the intervention period with an average of 2 cm in all three study groups. A decrease in the sum of four skinfolds was observed in children who followed the weight reduction intervention, yet not in children from the exercise or the control group. When maximal aerobic capacity was expressed per kg body weight, a nonsignificant increase for the exercise group was observed. Total caloric intake decreased after 12 weeks of caloric restriction. All specific nutrient intakes remained essentially unchanged. When expressed per daily caloric intake, only total fat intake decreased in the weight reduction group.

In Figure 6.3.1 mean levels of plasma total cholesterol, LDL - and HDL cholesterol are presented for all study groups. After 12 weeks of intervention mean total cholesterol was 161 mg/dl (SE 5.7) in the diet group, 169 mg/dl (SE 5.9) in the exercise group, and 184 mg/dl (SE 5.9) in the controls. Total cholesterol was lower in the diet ($p_1=0.01$) and in the exercise group ($p_1=0.05$), compared to the controls.

Table 6.3.3. Anthropometry, physical fitness and nutrient intake+ after 12 weeks.

	Exercise (*n* = 34)	*Control* (*n* = 33)	*Weight reduction* (*n* = 35)
Body weight (kg)	43.2 (1.3)	44.4 (1.4)	42.2 (1.1)*
Height (cm)	149.6 (1.6)	149.0 (1.5)	150.3 (1.4)
Sum of skinfolds (mm)	49 (3)	55 (4)	44 (3)*
VO_2max (l/min)	1.89 (0.05)	1.86 (0.06)	1.85 (0.05)
VO_2max/kg (ml/minkg)	44.1 (1.0)	41.9 (1.0)	44.3 (1.2)
Total calorie intake (kcal/day)	2294 (122)	2382 (93)	1781 (49)*
Total fat (g/kcal)	0.042 (0.001)	0.042 (0.001)	0.040 (0.001)#
Saturated fat (g/kcal)	0.0182 (0.0003)	0.0180 (0.0004)	0.0173 (0.0004)
Monounsaturated fat (g/kcal)	0.0159 (0.0004)	0.0158 (0.0004)	0.0153 (0.0005)
Polyunsaturated fat (g/kcal)	0.0070 (0.0004)	0.0076 (0.0004)	0.0062 (0.0003)
P/S ($kcal^{-1} * 10^2$)	0.020 (0.001)	0.021 (0.001)	0.023 (0.001)
Cholesterol (mg/kcal)	0.106 (0.005)	0.101 (0.004)	0.111 (0.003)
Linoleic acid (g/kcal)	0.0058 (0.0003)	0.0067 (0.0004)	0.0052 (0.0003)
Carbohydrates (g/kcal)	0.069 (0.002)	0.069 (0.003)	0.065 (0.002)
Mono- and disaccharides (g/kcal)	0.053 (0.002)	0.053 (0.001)	0.058 (0.001)
Polysaccharides (g/kcal)	0.123 (0.002)	0.123 (0.002)	0.124 (0.002)

+ Values are means with standard errors in parentheses
* p values are given for differences from base-line with controls as reference;
* $p_2 < 0.01$; ** $p_2 = 0.01$; # $p_2 = 0.03$

Mean levels of LDL cholesterol were lower after 12 weeks of intervention in the exercise (p_1=0.05) and in the diet group (p_1=0.01), compared to the children from the control group. No differences in mean levels of HDL cholesterol were found between the three study groups at the end of the intervention period. Compared to the controls, mean levels of triglycerides were lower in the diet group (78 mg/dl, SE 6.3, p_1<0.01) and lower in the exercise group (89mg/dl, SE 6.2, p_1=0.3). No differences in mean levels of HDL cholesterol subfractions and apolipoprotein A-I were observed between the study groups. Mean levels of apolipoprotein A-II were lower in the diet group (p_1=0.04), and mean apolipoprotein B levels were lower in the exercise (p_1=0.03) and in the diet group (p_1<0.01).

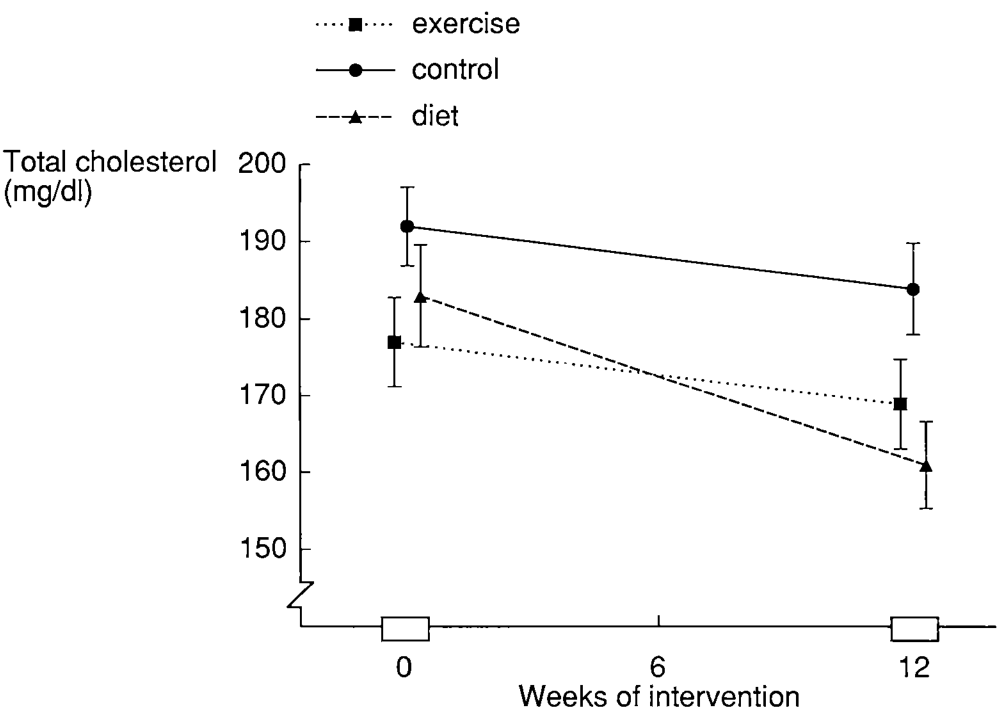

Figure 6.3.1. Plasma lipid and lipoprotein levels at base-line and after 12 weeks of intervention. Values are means with standard errors.

Changes in plasma lipids and lipoproteins from base-line in the intervention groups were calculated with the controls as reference group (Table 6.3.4). Children who followed the weight reduction intervention had total cholesterol levels which were lowered with 6.3% (11.5 mg/dl; 90% confidence limits: -21.9, -1.1; p_1=0.04), triglyceride levels with 2.3% (18.5 mg/dl; confidence limits: -35.8, -1.2; p_1=0.04) and apolipoprotein A-II levels in this group fell by 10.4% (5.1 mg/dl; confidence limits: -8.9, -1.3; p_1=0.02). No differences in changes in HDL cholesterol subfractions or apolipoprotein A-I and B could be found.

All analyses were performed for boys and girls separately, but these showed no difference in response between the two genders.

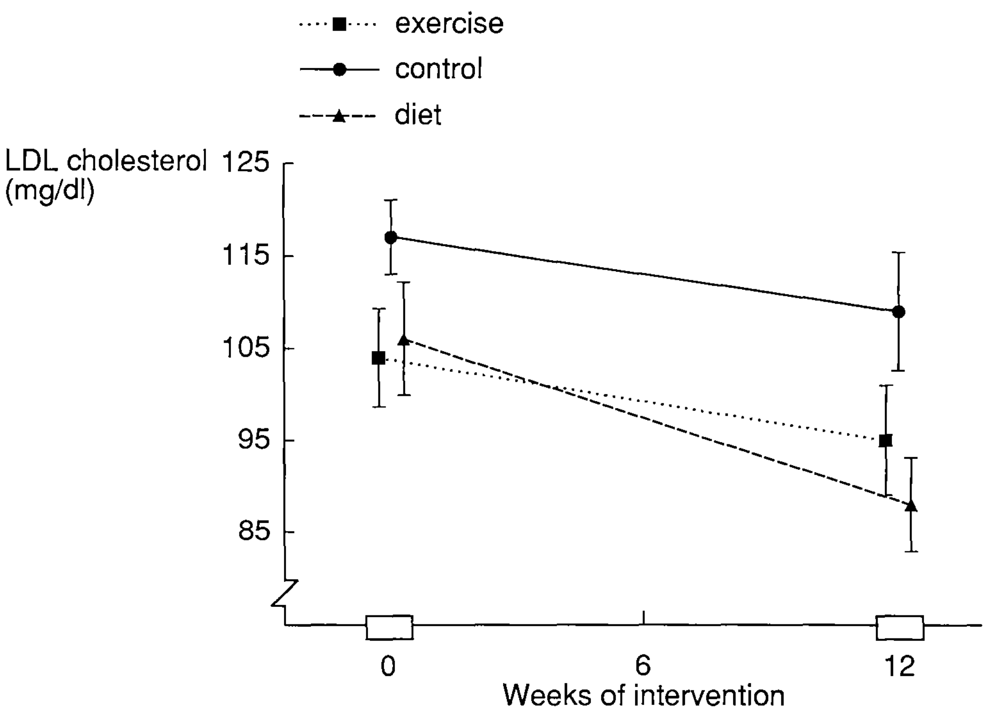

Figure 6.3.1. (cont.) Plasma lipid and lipoprotein levels at base-line and after 12 weeks of intervention. Values are means with standard errors.

Discussion

The main findings of this study in relatively overweight, 10 year old children are that total cholesterol, triglycerides and apolipoprotein A-II levels are reduced following moderate caloric restriction. Exercise intervention appears to have no effect on plasma lipids or lipoproteins.

Before these findings can be accepted, some characteristics of the study must be considered. The use of a food frequency questionnaire, filled in by the parents, could bias the results of the nutrient intake in the weight reduction group. Therefore, careful interpretation is necessary. Nonetheless, both children and their parents frankly discussed the adherence to the diet with the dieticians during the home visits. This information was used as an extra check on the food frequency questionnaires. The value of obtained data from questionnaires on food intake can be questioned.

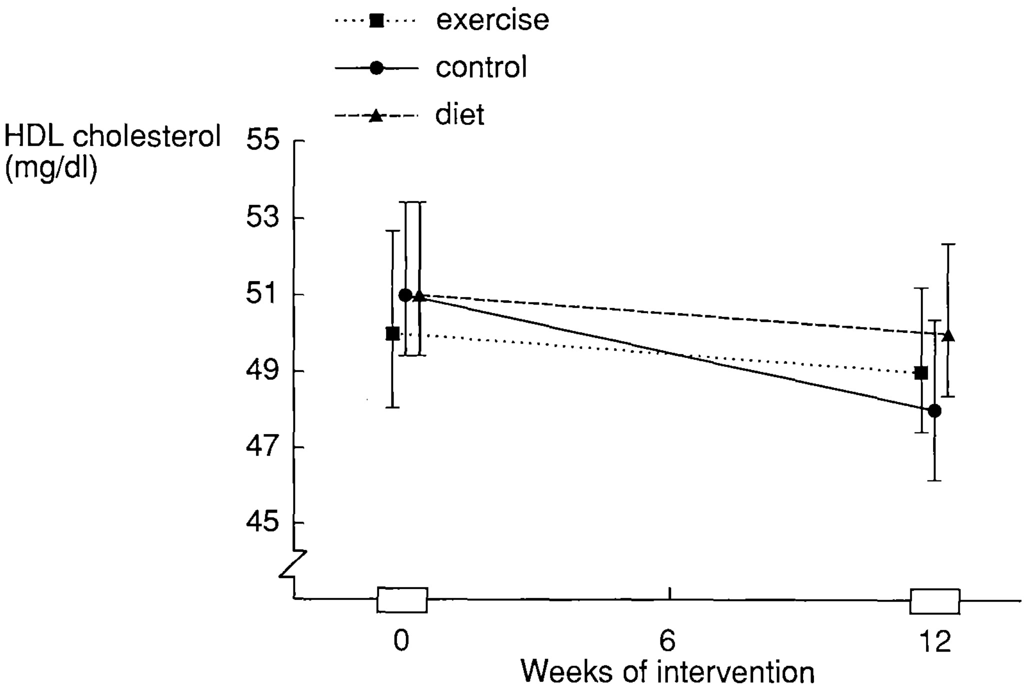

***Figure 6.3.1.** (cont.) Plasma lipid and lipoprotein levels at base-line and after 12 weeks of intervention. Values are means with standard errors.*

However, a high reproducibility and accuracy has been reported for specific foods and nutrient intakes (33) and after adjustment for total caloric intake, nutrient intakes assessed by questionnaires correlated more strongly with diet records (34). As in this type of study no blinding of the intervention could be achieved, all measurements were carried out by observers who were unaware of the study group of the participant. Furthermore, laboratory analyses were blinded and the children and their parents were not informed about the hypotheses studied until the trial was ended.

Although participation and intensity of the training during the exercise intervention were closely monitored with the heart frequency registration, a clear increase of maximal oxygen consumption could not be found. We studied other indirect parameters of physical fitness, as heart rate in rest, maximal heart rate achieved during the maximal exercise test, and running time on the treadmill and

Table 6.3.4. Net changes+ in plasma lipids and lipoproteins from base-line with the control group as reference for the total group.

	Exercise	*Weight reduction*
Plasma lipids		
Total cholesterol (mg/dl)	3.7 (- 6.7, 14.1)	-11.5 (-21.9, -1.1)
Triglycerides (mg/dl)	- 2.2 (-19.4, 12.6)	-18.5 (-35.8, -1.2)
Plasma lipoproteins		
LDL cholesterol (mg/dl)	2.2 (- 8.2, 12.6)	- 7.4 (-17.8, 3.0)
HDL cholesterol (mg/dl)	1.6 (- 2.4, 5.6)	3.1 (- 1.0, 7.2)
HDL_2 cholesterol (mg/dl)	- 0.7 (- 3.3, 1.9)	2.0 (- 0.6, 4.6)
HDL_3 cholesterol (mg/dl)	1.9 (- 1.6, 5.4)	1.3 (- 2.2, 4.8)
Apolipoprotein A-I (mg/dl)	- 2.6 (-10.2, 5.0)	- 3.8 (-11.4, 3.8)
Apolipoprotein A-II (mg/dl)	0.9 (- 2.9, 4.7)	- 5.1 (- 8.9, -1.3)
Apolipoprotein B (mg/dl)	0.2 (- 5.6, 6.0)	- 5.2 (-11.0, 0.6)

+ Values are means with 90% confidence intervals in parentheses

observed that these factors increased after intervention, but not statistically significant.

No effect on plasma lipids or lipoproteins, especially HDL cholesterol, could be observed for the exercise intervention group. Increases in HDL cholesterol have generally been after either prolonged or highly intensive endurance exercise in adults (35,36). Wood et al. reported that the magnitude of change in HDL cholesterol was highly associated with the amount of exercise performed (37). It could be that the frequency of exercise training during 12 weeks of 2 hours per week applied in our study, was not sufficient to increase either maximal oxygen uptake or HDL cholesterol levels.

Total cholesterol, triglycerides, and apolipoprotein A-II levels decreased in the children participating in the weight reduction program more than in the control subjects. These beneficial changes could result from a relative total body weight loss or a decrease in the sum of skinfolds or both. A change in body fat, determined by hydrostatic weighing, was related to a decrease in triglycerides, an increase of HDL cholesterol and its subfractions in overweight men participating in a one-year randomized trial (38). Levels of total and LDL cholesterol were not changed. Observational studies have reported an association of lipoproteins with obesity, and not so much with body weight (5,10,12). Nonetheless, a change in body weight per se could also result in the benefical changes observed.

Higher activities of lipoprotein lipase or a change in insulin-glucose metabolism could be part of the underlying mechanism (39,40). Also, the observed effect in the weight reduction group could result from changes in nutrient intake. Recently, one study reported an unequivocal relation between dietary fat intake and plasma cholesterol (41).

In summary, an intervention program of mild caloric restriction leading to no increase in body weight in children can result in a more favorable lipid profile. Moderate exercise intervention appears not to have any effect on plasma lipids and lipoproteins in overweight children.

Acknowledgement

We are indebted to the children and their parents for their dedicated contribution during the trial; to Heidi Mollée-Sijbrandij, Marjolein van den Bergh, Mariska de Vette for their specific contribution to the weight reduction group; to Ton de Bruyn, Elisabeth van Herpen, Jeanette Vergeer-Drop, René Vermeeren for laboratory assistance; to Hilda Kornman-van den Bosch, Anneke van der Muil-Houwing, Hanneke van Meurs, Ria Rijneveldshoek, Gitte Buitelaar, Linelle Deunk, Baya Hutten, Monica Veeger for their work at the research center; to Marcel Eijgermans and Robert Rosier for assistance with data-analysis. This study was supported by General Biscuits, The Netherlands, and Riedel Drinks, Ede, The Netherlands.

References

1. Aristimuno GG, Foster TA, Voors AW, Srinivasan SR, Berenson GS. Influence of persistent obesity in children on cardiovascular risk factors: The Bogalusa Heart Study. Circulation, 1984;69:895-904.
2. Garn SM, LaVelle M. Two-decade follow-up of fatness in early childhood. Am J Diseases in Children, 1985;139:181-5.
3. Stark O, Atkins E, Wolff OH, Douglas JWB. Longitudinal study of obesity in the National Survey of Health and Development. Br Med J 1981;283:13-7.
4. Charney E, Goodman HC, Mcbride M, Lyon B, Pratt R. Childhood antecedents of adult obesity. Do chubby infants become obese adults? N Eng J Med 1976;295:6-9.
5. Berenson GS, Epstein FH. Conference on blood lipids in children: Optimal levels for early prevention of coronary artery disease. Prev Med 1983;12:741-7.
6. Khoury P, Morrison JA, Kelly K, Mellies M, Horvitz R, Glueck CJ. Clustering and interrelationships of coronary heart disease risk factors in schoolchildren, ages 6-19. Am J Epidemiol 1980;112:524-38.
7. Glueck CJ, Heiss G, Morrison JA, Khoury P, Moore M. Alcoholintake, cigarette

smoking and plasma lipids and lipoproteins in 12-19-year-old children. The collaborative lipid research clinics prevalence study. Circulation 1981;64 (suppl III):48-56.
8. Laskarzewski P, Morrison JA, Mellies MJ, et al. Relationships of measurements of body mass to plasma lipoproteins in schoolchildren and adults. Am J Epidemiol 1980;111:395-406.
9. Berenson GS, Srinivasan SR, Frank GC, Webber MPH, Webber LS. Serum lipid and lipoprotein in infants and children and their relationship with diet. Nutr Child Health 1980:73-94.
10. Yamamoto A, Horibe H, Sawada S, et al. Serum lipid levels in elementary and junior high school children and their relationship to relative weight. Prev Med 1988;17:93-108.
11. Orchard TJ, Rodgers M, Hedley AJ, Mitchell JRA. Serum lipids in a teenage population: geografic, seasonal and familial factors. Int J Epidemiol 1981;10:161-70.
12. Freedman DS, Burke GL, Harsha DW, Srinivasan SR, Cresanta JL, Webber LS, Berenson GS. Relationship of changes in obesity to serum lipid and lipoprotein changes in childhood and adolescence. JAMA 1985;254:515-20.
13. Castelli WP, Garrison RJ, Wilson PWF, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham study. JAMA 1986;256:2835-8.
14. The Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events. J Chron Dis 1978;31:225-306.
15. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356222 primary screenees of the Multiple Risk Factor Intervention trial. JAMA 1986;256:2823-8.
16. Wallace RB, Anderson RA. Blood lipids, lipid-related measures, and the risk of atherosclerotic cardiovascular disease. Epidemiol Rev 1987;9:95-119.
17. Man de SA, Grobbee DE, Stiphout van WAHJ, Valkenburg HA, Hofman A. Serum lipids, lipoproteins and physical fitness in childhood. Am J Epidemiol (in press).
18. Man de SA, Grobbee DE, Hofman A. A study on blood pressure and physical fitness in childhood in the Netherlands. J Hypertension 1989;7:430.
19. Léger L, Thivierge M. Heart rate monitors: validity, stability, and functionality. Phys Sportsmed 1988;16:50-7.
20. Houten van M. 'Door dik en dun.' A health education program for overweight children. Vlaardingen, 1981.
21. Epstein LH, Masek BJ, Marshall WR. A nutritionally based school program for control of eating in obese children. Behav Ther 1978;9:766-88.
22. Epstein LH, Wing RR, Koeske R, et al. Child and parent weight loss in family-based behavior modification programs. J Consult Clin Psychol 1981;49:674-85.
23. Van Gent CM, Van der Voort HA, De Bruyn AM, Klein F. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-51.

24. Burstein M, Scholnick HR, Morfin R. Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. J Lipid Res 1970;11:583-95.
25. Grove TH. Effect of reagent pH on determination of high-density lipoprotein cholesterol by precipitation with sodium phosphotungstate-magnesium. Clin Chem 1979;25:560-4.
26. Gidez LI, Miller GJ, Burstein M, Sagle S, Eder HA. Separation and quantification of subclasses of human plasma high density lipoproteins by a simple precipitation procedure. J Lipid Res 1982;23:1206-23.
27. Cheung MC, Albers JJ. The measurement of apolipoprotein A-I and A-II levels in men and women by immunoassay. J Clin Invest 1977;60:43-50.
28. Giegel JL, Ham AB, Clema W. Manual and semi-automated procedures for measurement of triglycerides in serum. Clin Chem 1975;21:1575-81.
29. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973;85:546-62.
30. Åstrand PO, Rodahl K. Textbook of work physiology. Physiological bases of exercise. New York: McGraw-Hill Book Company, 1986:354-91.
31. Bar-Or O. Procedures for exercise testing in children. In: Katz M, Stiehm ER, eds. Pediatric sports medicine for the practitioner. New York: Springer-Verlag, 1983:305-41.
32. Commissie N.C.V.. Voorlichtingsbureau voor de voeding. N.E.V.O. tabel (Dutch computerized food composition table). 's Gravenhage, 1989.
33. Sampson L. Food frequency questionnaires as a research instrument. Clin Nutrition 1985;4:171-8.
34. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51-65.
35. Gilliam TB, Freedson PS. Effects of a 12-week school physical fitness program on peak VO_2, body composition and blood lipids in 7 to 9 year old children. Int J Sports Med 1980;1:73-78.
36. Sasaki J, Shindo M, Tanaka H, Ando M, Arakawa K. A long-term aerobic exercise program decreases the obesity index and increases the high density lipoprotein cholesterol concentration in obese children. Int J Obes 1987;11:339-45.
37. Wood PD, Haskell WL, Blair SN, Williams PT, Krauss RM, Lindgren FT, Albers JJ, Ho PH, Farquhar JW. Increased exercise level and plasma lipoprotein concentrations: a one-year randomized, controlled study in sedentary middle-aged men. Metabolism 1983;32:31-9.
38. Wood PD, Stefanick ML, Dreon DM, Frey-Hewitt B, Garay SC, Williams PT, Superko HR, Fortmann SP, Albers JJ, Vranizan KM, Ellsworth NM, Terry RB, Haskell WL. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared to exercise. N Engl J Med 1988;319:1173-9.
39. Ostlund RE, Staten M, Korth WM, Schultz J, Malley M. The ratio of waist-to-hip

circumference, plasma insulin level, and glucose intolerance as independent predictors of the HDL2 cholesterol level in older adults. N Eng J Med 1990;322:229-34.

40. Williams PT, Krauss RM, Vranizan KM, Wood PDS. Changes in lipoprotein subfractions during diet-induced and exercise-induced weight loss in moderately overweight men. Circulation 1990;81:1293-304.

41. Thorogood M, Roe L, McPherson K, Mann J. Dietary intake and plasma lipid levels: lessons from a study of the diet of a health conscious group. B Med J 1990;300:1297-301.

CHAPTER 7

GENERAL CONCLUSIONS

The power and beauty of science do not rest upon infallibility, which it has not, but on corrigibility, without which it is nothing (H.E. Gruber. The origin of the origin of species: review of Darwin and the mysterious mr. X).

7. GENERAL CONCLUSIONS

This thesis focuses on physical fitness as a determinant of cardiovascular risk factors in childhood. In this chapter the design of the described studies, and the methods used will be discussed. The study results, as presented in the preceding chapters, will be annotated and some suggestions for further research in the perspective of prevention of atherosclerosis will be given.

Study design

Two types of study formed the basis of the work presented in this thesis, i.e. an observational and an experimental study. A potential problem with a cross-sectional study is selection bias in the distribution of study variables in its study population (1,2). It is possible that we selected children with a very high or low blood pressure level or lipoprotein profile. Nonetheless, levels were quite comparable with other studies, as could be said of the levels of physical fitness. In addition, the population who participated in the observational study was a large group of 1,558 children who were randomly selected and response rates were high, thus reducing the possibility of selection bias.

Observational studies can be categorized as follow-up or case-control studies. Although these type of studies have often been applied in medicine and can serve to develop hypotheses, observational studies cannot provide the degree of control to maintain the internal validity of the study as under experimental circumstances. The ultimate goal of an experiment is to isolate the one determinant that is considered relevant to the occurrence relation under study and control all other factors that would affect the outcome parameter. Therefore, trials are often regarded as the 'gold standard' in cause-effect studies (3,4). With respect to the internal validity of the study, randomization is of utmost importance (5). In our experimental study on blood pressure randomization led to satisfactory baseline comparability between the groups. However, for plasma lipids and lipoproteins some differences in base-line levels between the three study groups were observed, especiallly for apolipoprotein B. We performed an additional analysis with adjustments for baseline levels, but the results described in chapter 6.3 did not materially alter. As already discussed in chapter 6.2 the experimental study could not be performed double-blind. This may have influenced the results, especially for blood pressure. But as the observers were unaware of the intervention status of the participants and blood pressure was measured with an automatic device, we believe that optimal single-blindness was achieved. In addition, the participants were not informed on the exact hypotheses studied until the study was finished.

Study measurements

This thesis concerns physical fitness at a young age. In all studies, daily physical activity was also measured by questionnaire, covering the activity level in the past three months. A preliminary analysis of these data indicates no association between daily physical activity and cardiovascular risk factors. These results could be due to measurement error, which dilutes the observed association with daily physical activity. A very accurate method to measure daily physical activity is the double labelled water technique as described by Schoeller (6). However, some major disadvantages of this method are high costs and the use of isotopes. In addition, daily physical activity and physical fitness showed very low correlations in our study. As mentioned earlier, either daily physical activity was measured inadequately or other aspects of activity are reflected in physical fitness compared to measures of daily physical activity. Several theories, as discussed in chapter 5, could be possible. On the one hand, physical fitness could be viewed as an intermediate factor between daily physical activity and cardiovascular risk factors. Because we studied relatively young children a large amount of daily physical activity could be necessary to improve physical fitness. On the other hand, physical fitness could be mainly genetically determined in this age group and be largely independent of the amount of physical activity.

Study results

In our study physical fitness was related to diastolic blood pressure in childhood. This conclusion tends to support the results reported in literature so far, as described in the review presented in chapter 2.1. Intervention by an exercise program in overweight children resulted in a fall in systolic blood pressure without a change in physical fitness or body weight. No relation between physical fitness and serum lipids or lipoproteins was observed. Probably, when these children will come into puberty, an association with the lipid profile may be found. Also, no change in lipids or lipoproteins was found after moderate exercise intervention. Although the level of exercise was highly controlled, no increase of maximal aerobic capacity was observed. Possibly, a longer period of exercise or a higher intensity level is needed to achieve an increase in physical fitness to be determined by a change in maximal aerobic capacity. A relative reduction of body weight through total caloric restriction resulted in a decrease in systolic blood pressure, and in total cholesterol, triglycerides and apolipoprotein A-II in overweight children. The hemodynamic measurements performed in our non-experimental study support the hypothesis of a hyperkinetic state in the early phase of a gradual rised blood pressure that may ultimately lead to hypertension. Perhaps even more important, higher levels of physical fitness appear to be accompanied by cardiac morphological changes.

Conclusions

As illustrated by the work presented in this thesis, studies on the association between the change in physical fitness and the change in blood pressure and serum lipids could provide insight in the aetiology of cardiovascular risk factors at a young age. Apart from the intervention studies, that are of limited duration by nature, data are needed from long term observation to assess the physiologic association between these dynamic characteristics. In addition, studies with accurately measured daily physical activity, especially in relation to serum lipids and lipoproteins, should be performed.

Apart from aetiologic information, the results of our studies point at certain prospects for prevention. The so-called high risk treatment approach, aiming at individuals with elevated levels of cardiovascular risk factors and the total population approach, aiming at a general shift of the distribution of cardiovascular risk factors, do not exclude eachother in prevention of atherosclerosis (7). Non-pharmacological intervention, especially at a young age, could aim to create a favorable environment in order to achieve lower levels of the distribution of cardiovascular risk factors. Nonetheless, high risk strategies should be applied to subjects at the upper end of the distribution, depending on the origin of their cardiovascular risk factor level and on their age.

Finally, overweight children should be monitored with regard to tracking and de-tracking of cardiovascular risk factors by measuring blood pressure and lipids yearly, especially when there is a positive family history on cardiovascular disease.

References

1. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiological research: principles and quantitative methods. New York: Van Norstrand Reinhold Company Inc, 1982;40-51.
2. Hennekens CHH, Buring JE. Epidemiology in medicine. Mayrent SL, ed. Boston: Little, Brown and Company, 1987;101-32.

3. Feinstein AR, Horwitz RI. Double standards, scientific methods, and epidemiologic research. N Eng L Med 1982;307:1611-8.
4. Rothman KJ. Modern epidemiology. Boston: Little, Brown and Company, 1986;51-77.
5. Box GEP, Hunter WG, Hunter JS. Statistics for experimenters. An introduction to design, data-analysis and model building. New York: John Wiley and Sons, 1978:93-106.
6. Schoeller DA. Energy expenditure from double labelled water: some fundamental consideratios in humans. Am J Clin Nutr 1983;38:999-1005.
7. Rose G. Strategy of prevention: lessons from cardiovascular disease. Br Med J 1981; 282:1847-51.

CHAPTER 8

BLOOD PRESSURE IN CHILDHOOD:

POOLED FINDINGS OF SIX EUROPEAN STUDIES

8. BLOOD PRESSURE IN CHILDHOOD: POOLED FINDINGS OF SIX EUROPEAN STUDIES.

Introduction

There is growing agreement on the view that primary hypertension, one of the most important risk factors for cardiovascular disease, is rooted early in life (1-5). This notion has fostered the interest in blood pressure in childhood. Of particular interest is the question which levels of blood pressure in childhood are "normal" and at what level a child's blood pressure could be considered relatively high compared to its age and sex category. No systematic data on blood pressure in childhood across the various European countries, based on a standardized protocol, are available. So far only reference values for blood pressure in North-American children have been published (6,7). In this pooled analysis percentile values, obtained from six studies conducted in North-West European countries, are presented.

Methods

Study populations and measurements

Combining six population based studies, blood pressure was measured in a total number of 28,043 children, aged 4-19 years. An overview of the studies with details concerning study subjects and measurement techniques is presented in Table 8.1. A short description of each study will be given hereafter.

Berlin-Bremen, FRG. From 1983 until 1986 the Berlin-Bremen study was carried out. For the present analysis data from the first year of investigation are used (1983). During that year, 2,050 subjects of the ages 11-17 years were eligible from 22 schools in Bremen and Berlin. The participation rate was 69% and blood pressure values of 1,302 children were included in the pooled analysis. Blood pressure was measured at the right arm of a sitting subject with a random zero sphygmomanometer (8). Three different types of cuff were used: 9x18, 12x23, and 14x28 cm, according to the circumference of the arm.

Cologne, FRG. In 1975 the first cross-sectional survey of 6,302 adolescents, aged 15-19 years, was conducted in 41 schools in the city of Cologne. In 1976 3,692 adolescents, still studying at the same schools, were invited for re-examination. The participation rate was 81%. For the present analysis, data from 2,934 children of this follow-up study have been used. Blood pressure was measured twice by medical technicians in sitting position with a standard cuff size of 12.5x28 cm. In general a London School of Hygiene sphygmomanometer, type Mark IV, was used (9).

Table 8.1. General characteristics of the studies included in the analysis.

Source	*Age (yrs)*	*Boys n*	*Girls n*	*Total n*	*Device*	*Position during measurement*	*Cuffsize* (cm^2)	*Population*
Berlin-Bremen	11-17	731	571	1,302	RZ	sitting RA	9x18	school
							12x23	
							14x28	
Cologne	15-19	1,353	1,581	2,934	LSH	sitting RA	12,5x28	school
Copenhagen	6-17	447	451	898	RZ	sitting RA	6x20	school
							9x28	
							12x35	
Essen	4-18	751	720	1,471	LSH	sitting RA	8x20	school
							12x25	open
Nancy	4-17	8,647	8,420	17,067	MS	supine RA, LA	9x22	open
							12x26	
Zoetermeer	5-19	2,198	2,173	4,371	RZ	sitting LA	10x23	open
							14x23	

RZ, random zero sphygmomanometer; LSH, London School of Hygiene sphygmomanometer; MS, standard mercury sphygmomanometer; RA, right arm; LA, left arm.

Copenhagen, Denmark. In 1984, a sample of 1,400 children, aged 6-18 years, was drawn by selecting parents of these children from the census register of the municipality of Copenhagen. They represent a wide range of socio-economic backgrounds. Partipicipation rate was 64%. Data from 898 youngsters are used in the analysis. Blood pressure was examined after five minutes of rest, at the right arm in sitting position with a random zero sphygmomanometer. Cuff sizes varied from 6x20 to 12x35 cm.
Essen, FRG. In 1977 the Essen-study was conducted, in which 433 pre-schoolchildren were randomly selected from a total of 6,000. Schoolchildren were selected from 20 different schools, representative for the various types of school found in this city. Eventually 306 pre-schoolchildren, aged 4-6 years, and 1,165 schoolchildren, aged 7-18 years, participated. Response rates were 70.7% and 97%, for pre-school- and schoolchildren respectively. The London School of Hygiene sphygmomanometer was used to measure blood pressure on the right arm of the sitting subject. The cuff covered at least 2/3 of the length of the upperarm.
Nancy, France. At the Preventive Medicine Center in Nancy blood pressure measurements were performed between 1977 and 1979. Families were selected at random and 17,067 children of these families participated in the study. The age of the children varied from 4 to 17 years. After five minutes of rest, while the subject was lying down, blood pressure was measured with a mercury sphygmomanometer. The cuff completely encompassed the circumference of the upperarm and covered 2/3 of its length.
Zoetermeer, the Netherlands. From 1975 to 1979 5,670 children and adolescents, aged 5-19 years, were invited to participate in a study of blood pressure and other risk factors for cardiovascular diseases. Participants were residents of the city of Zoetermeer. The participation rate was 82%. In 4,371 subjects blood pressure was measured with a random zero sphygmomanometer on the left arm by paramedical observers after a period of 15 minutes rest. In general the largest cuff comfortably encircling the arm was used, implying that for the ages of 5-9 years a cuff of 10x23 cm and for the ages of 10 years or over a cuff of 14x23 cm was applied.

Data-analysis

In general the first blood pressure reading in each individual child was used for calculation of the percentile values from the pooled data. An exception is the Cologne-study, of which only measurements of the second year of investigation were available. Systolic pressure is based on the appearance of the first Korotkoff phase and diastolic pressure on the fifth phase at a precision of 2 mmHg. Body height (in cm) was measured with the subjects wearing indoor clothes, without shoes.

The 5th, 10th, 25th, 50th, 75th, 90th, and 95th centile of the systolic and diastolic blood pressure are provided, by age in full years and by height in categories of 5 cm.

For the purpose of pooling the data, the centile values, means and standard deviations have been weighed by the number of participants in each study. In the high and low categories of age and height, only data on relatively small numbers were available. Therefore, if the number of a particular study within one of the age and height categories was less than 20, only the 50th centile and the mean blood pressure value of this particular study were used in the pooled estimate. Also, if the total number of participants of the pooled studies in these strata did not exceed 25, the category was not included in the presentation. This has resulted in slight discrepancies in total number of participants shown by age and by height categories.

The curves have been smoothed by fitting a 4th order polynomial model of blood pressure on, age and height, respectively, using multiple regression analysis (10).

Results

The pooled data are presented as the 5th, 10th, 25th, 50th, 75th, 90th, and 95th centile. For boys, the age-specific centiles of systolic and diastolic pressure, are shown in the Figures 8.1 and 8.2, and for girls in the Figures 8.3 and 8.4. The height-specific centile values of systolic and diastolic blood pressure are presented in the Figures 8.5 and 8.6 for boys, and in the Figures 8.7 and 8.8 for girls.

Discussion

This analysis presents the pooled data of six different population based North-West European studies on blood pressure levels in 28,043 children. In order to compare a child's individual blood pressure with its age and sex category, blood pressure measurements of a sufficiently large group of unselected peers are needed, which have been obtained by a similar method as applied in measuring the child's own blood pressure. Blood pressure increases with age, occurring as early as the neonatal period, as well in association with growth and development (11-13). Therefore, the percentile values presented are given age- and height-specific for boys and girls separately.

The studies show differences in centile and mean levels. These may be due to differences in study population, measurement technique and circumstances under which the measurement took place. It is hard to achieve complete standardization, as there are numerous factors that may influence blood pressure and its measurement.

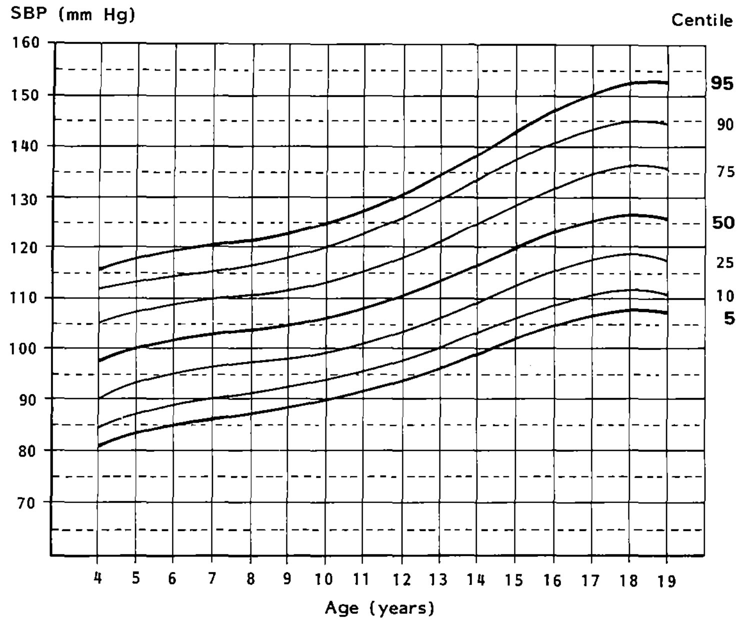

Figure 8.1. Age-specific percentiles of systolic blood pressure (SBP) in boys.

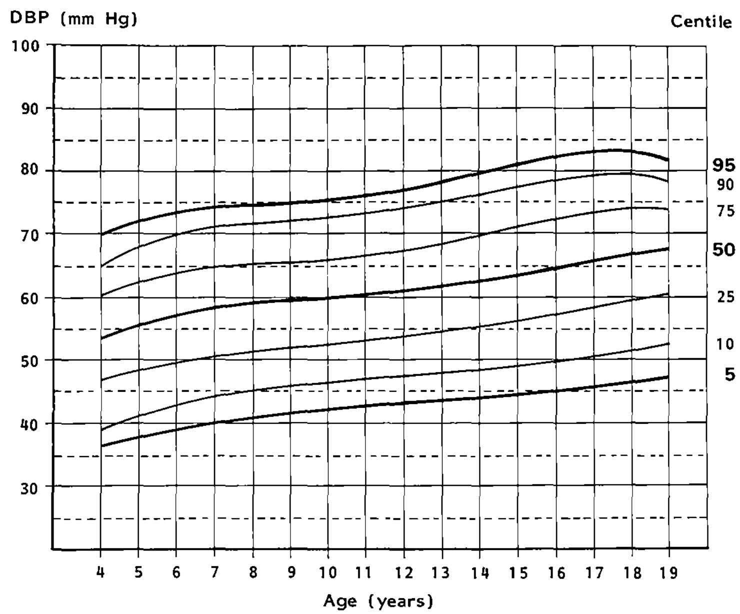

Figure 8.2. Age-specific percentiles of diastolic blood pressure (DBP) in boys.

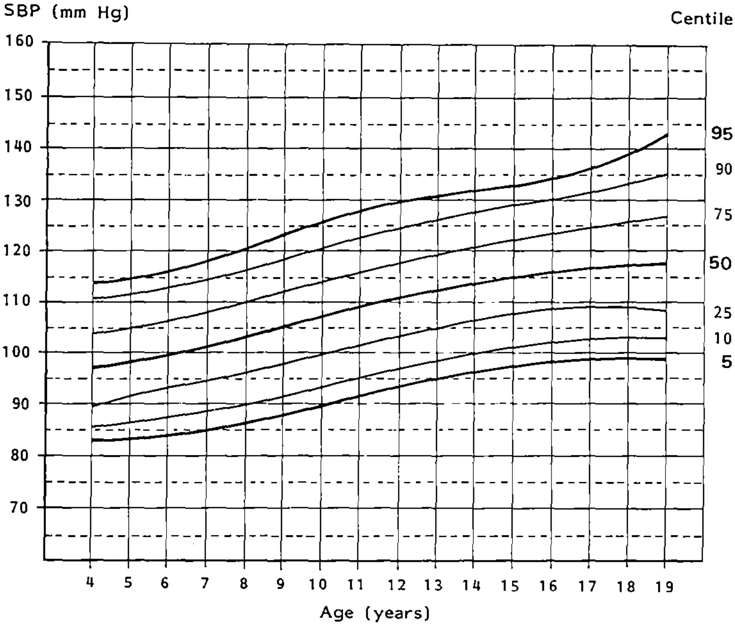

Figure 8.3. Age-specific percentiles of systolic blood pressure (SBP) in girls.

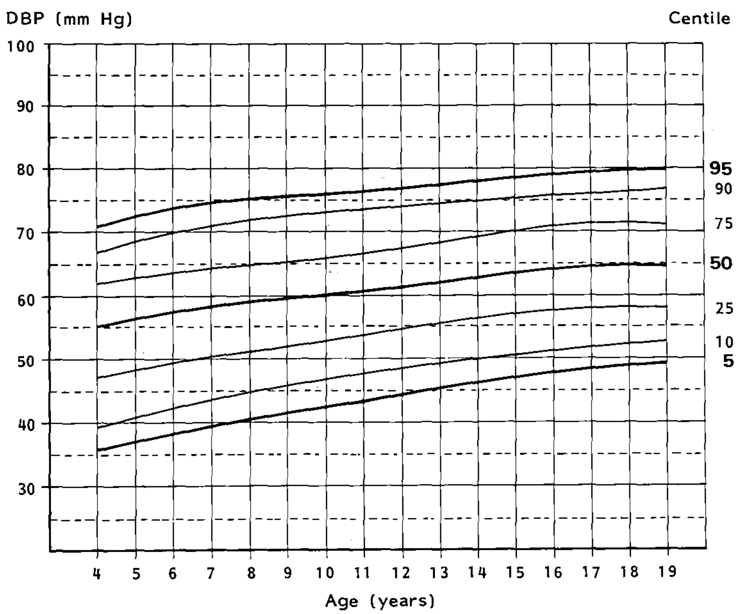

Figure 8.4. Age-specific percentiles of diastolic blood pressure (DBP) in girls.

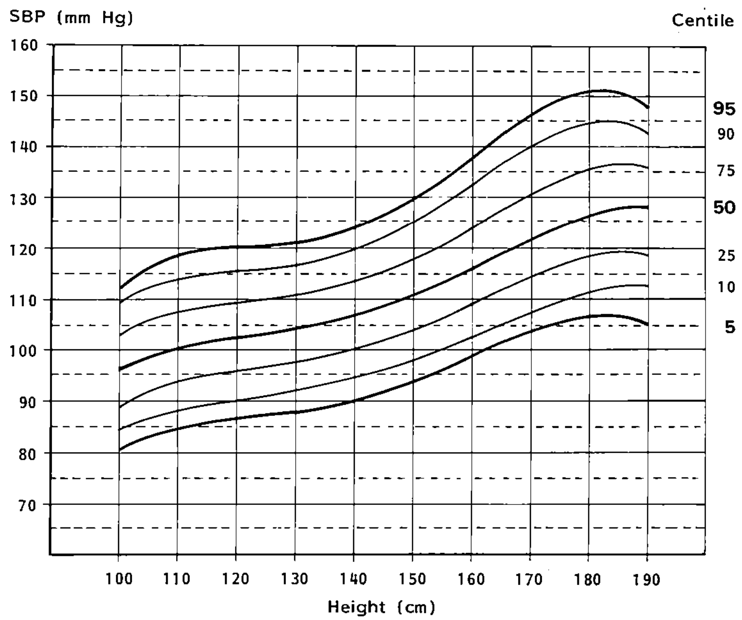

Figure 8.5. *Height-specific percentiles of systolic blood pressure (SBP) in boys.*

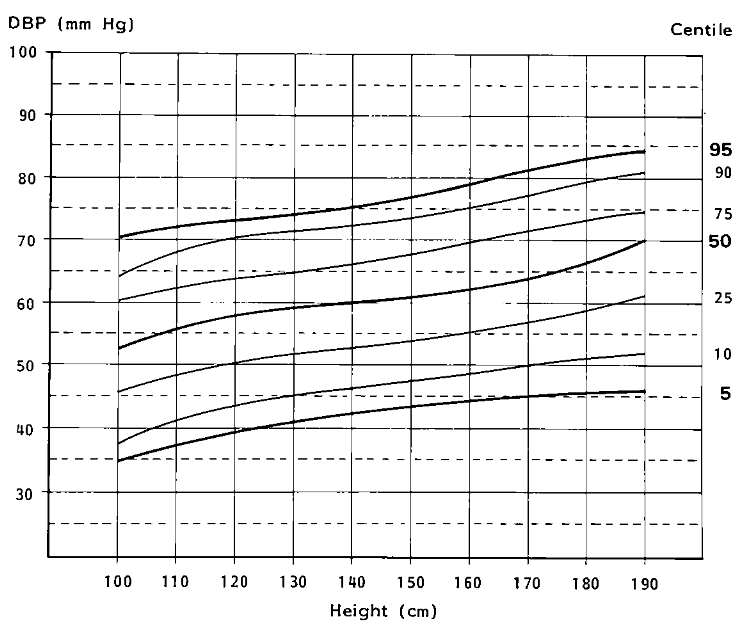

Figure 8.6. *Height-specific percentiles of diastolic blood pressure (DBP) in boys.*

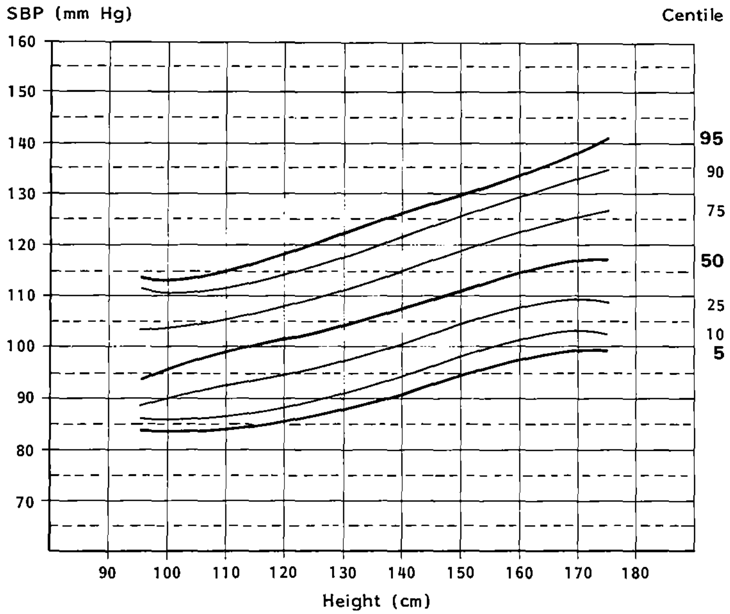

Figure 8.7. Height-specific percentiles of systolic blood pressure (SBP) in girls.

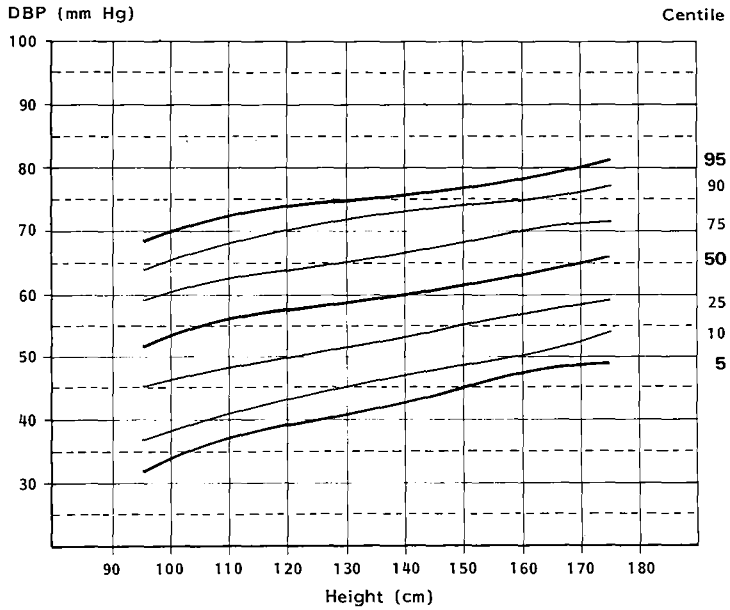

Figure 8.8. Height-specific percentiles of diastolic blood pressure (DBP) in girls.

With regard to this compilation of blood pressure values in children the differences in measurement technique are of particular importance. In the Nancy-study blood pressure has been measured with the children supine. This could be one explanation for the relative high values of mean systolic blood pressure, revealed in this study. An additional analysis was performed to compare the mean blood pressure levels of the Nancy study with the other studies. However, no difference in systolic or diastolic blood pressure levels could be found. Also, across the studies different cuff sizes were used (14), although usually the medium size of 12x23 cm has been employed. Blood pressure was measured with three different devices, the random zero sphygmomanometer, the London School of Hygiene device, and the standard mercury sphygmomanometer. Yet, the principle, on which blood pressure measurement is based, is similar for these devices and a relatively high agreement between these sphygmomanometers has been found (8,9,15,16).

The centile curves presented are not specified according to body weight. Data for this analysis were not available. Although body weight is related to blood pressure (11) and appears to be a predictor of rise in blood pressure (16,18), the mechanisms behind this association are not completely clear. For the purpose of estimating a child's physiological blood pressure level, height would probably be a better indicator of growth than body weight (19).

The American Task Force for Blood Pressure Control has provided reference values of blood pressure, derived from 9 studies with a total number of children participating of circa 70,000 and conducted in a similar time period (7). Comparing blood pressure values with the presented European values, it appears that in American children the centile and mean values of systolic blood pressure are lower. There is an average difference of 6 mmHg for both girls and boys (Figure 8.1 and 8.3). Comparison of diastolic blood pressure, based on the fifth Korotkoff phase, is limited to the age group of 13 years and older. Centile values in American children are on average 3 mmHg higher and mean values are quite similar (Figure 8.2 and 8.4). This phenomenon could result from a number of factors, especially from differences between the populations in characteristics related to blood pressure level and differences in the methods used for generating percentile values.

Guidelines for detecting children with high blood pressure have been formulated by a European Working Committee on blood pressure in children (20). These guidelines correspond to a large degree with those formulated by the American Task Force on Blood Pressure Control (7). Figure 8.9 shows a schematic representation of the proposed approach. All children who have a blood pressure above the 95th centile,

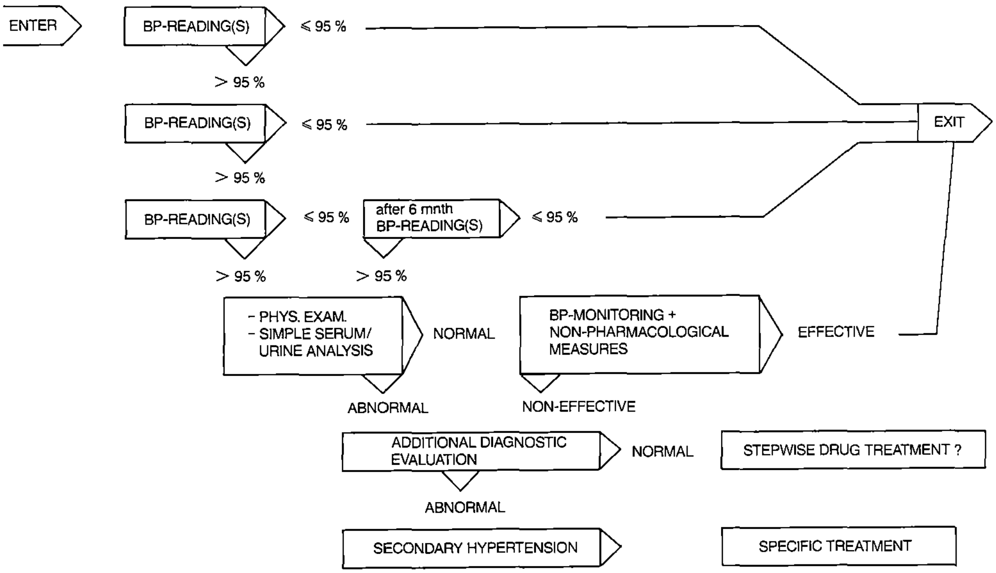

Figure 8.9. *Schematic representation of the detection and management of children with elevated blood pressure (BP) levels. Adapted from (21) with permission.*

should be remeasured at least twice in the same standardized protocol. If the blood pressure levels tend to remain above the 95th centile, medical history and physical examination, combined with supplementary laboratory assessment of blood urea nitrogen, creatinine and uric acid and urinary albumin and sediment have to be carried out. If abnormalities are found, a further search for secondary causes of hypertension forms the next step. If no abnormalities are found, blood pressure monitoring and non-pharmacological intervention, including weight reduction, physical conditioning and dietary modification (22), may be initiated. If these measures are insufficient, additional diagnostic evaluation may be executed. When abnormalities are found, secondary hypertension might be present. If not, one could consider stepwise drug treatment, depending on the level of the blood pressure, supplemented with non-pharmacological means of intervention (23). This, however, remains subject of debate in children and needs to be studied in more detail before advocated on a large scale (24).

To detect children and youngsters with a relatively high blood pressure and to monitor and study the blood pressure levels in the first decades of life, the percentile charts presented here may be used.

Acknowledgement

We gratefully acknowledge the contribution of Dr. P. Allhoff, Dr. M. Appleyard, Dr. F. Müller, Mrs. Y. Bekker-Wilthagen and Mr. L. Muller to this work. We thank Mr. P. Mulder for statistical advice.

References

1. Berenson GS, McMahan C, Voors AW, et al. Cardiovascular risk factors in children. The early natural history of atherosclerosis and essential hypertension. New York: Oxford University Press, 1980.
2. Clarke WR, Schrott HG, Leaverton PE, Connor WE, Lauer RM. Tracking of blood lipids and blood pressure in school age children: the Muscatine study. Circulation 1978;58:626-34.
3. Giovannelli G, New MI. Hypertension in children and adolescents. New York: Raven Press, 1981.
4. Labarthe DR. Blood pressure studies in children throughout the world. In Mild Hypertension edited by Gross F, Strasser T. New York: Raven Press, 1983, pp 85-96.
5. WHO Study Group. Blood pressure studies in children. Technical Report Series. Geneva: 1985.
6. Report of the Task Force on blood pressure control in children. Pediatrics 1977;59:797-820.
7. Report of the Second Task Force on blood pressure control in children-1987. Pediatrics 1987;79:1-25.
8. Wright BM, Dore CF. A random zero sphygmomanometer. Lancet 1970;1:337-8.
9. Rose GA, Holland WW, Crowley EA. A sphygmomanometer for epidemiologists. Lancet 1964;i:296-300.
10. Kleinbaum DG, Kupper LL, Muller KE. Applied regression analysis and other multivariable methods. Boston: PWS-Kent Publishing Company, 1988, pp 228-60.
11. Szklo M. Epidemiologic patterns of blood pressure in children. Epid Rev 1979;1:143-69.
12. Thell GS. Cardiovascular disease risk factors related to sexual maturation: The Oslo youth study. J Chron Dis 1985;38:633-42.
13. Hofman A, Adams LL. Blood pressure and age. In: Mild Hypertension: from trials to practice. Strasser T, Ganten D, eds. New York: Raven Press, 1986, pp 257-65.
14. Whincup PH, Cook DG, Shaper AG. Blood pressure measurement in children: the importance of cuff bladder size. J Hypertension 1989;7:845-50.
15. Hunyor SN, Flynn JM, Cochineas C. Comparison of performance of various sphygmomanometers with intra-arterial blood pressure readings. Br Med J 1978;2:159-62.
16. Labarthe DR, Hawkins CM, Remmington RD. Evaluation of performance of selected devices for measuring blood pressure. Am J Cardiol 1973;32:546-3.
17. Clarke WR, Woolson RF, Lauer RM. Changes in ponderosity and blood pressure in childhood: the Muscatine study. Am J Epidemiol 1985;124:195-206.
18. Visser MC, Grobbee DE, Hofman A. Determinants of rise in blood pressure in

normotensive children. J Hypertension 1987;5:367-70.

19. Voors AW, Harsha DW, Webber LS, Berenson GS. Relation of blood pressure to stature in healthy young adults. Am J Epidemiol 1982;115:833-40.
20. Recommendations for management of hypertension in children and adolescents. Clin and Exp Hypertension 1986;A8:901-18.
21. Grobbee DE, Hofman A. Non-pharmacological intervention of blood pressure in the young. In: The early pathogenesis of primary hypertension. Hofman A, Grobbee DE, Schalekamp MAHD, eds. Amsterdam: Elsevier Science Publishers, 1987, pp 37.
22. Cardiovascular risk factors in childhood: epidemiology and prevention. Hetzel BS, Berenson GS, eds. Amsterdam: Elsevier, 1987, pp 101-241.
23. Berenson GS, Voors AW, Webber LS, et al. A model of intervention for prevention of early essential hypertension in the 1980s. Hypertension 1983;5:41-53.
24. Jesse MJ. "Early" essential hypertension, prevention, intervention. Hypertension 1983;5:54-5.

CHAPTER 9

SUMMARY

9. SUMMARY

The studies on physical fitness in children as described in this thesis address the following questions: (1) is there a relation between physical fitness and cardiovascular risk factors, notably blood pressure and serum lipids and lipoproteins, at a young age? (2) what is the effect of increase of exercise and body weight reduction on blood pressure and the lipoprotein profile in overweight children, who tend to develop unfavorable levels of their cardiovascular risk factors, (3) and what are the possibilities early in life for prevention of future heart and vascular diseases?

Results from published studies on blood pressure and physical fitness in children and adolescents were reviewed. Lower blood pressure levels were found in children with higher levels of physical fitness, mainly in boys. The observed association seemed not to depend on age and method to assess physical fitness, but could be gender related. In addition the association between daily physical activity and blood pressure in youngsters was studied. No relation was observed between daily physical activity and blood pressure, which appeared not to depend on the method used to assess daily physical activity. Experimental results from multiple factor intervention trials, including daily physical activity, showed a decrease in blood pressure after one year of intervention. Also a decrease in blood pressure, mainly diastolic, was found after intervention on physical fitness (chapter 2.1).

Recent studies on determinants of lipids and lipoproteins in the young were reviewed, with special reference to the relation of the lipoprotein profile with daily physical activity and physical fitness. Obesity was shown to have an unfavorable relation with lipids and lipoproteins. This was to a lesser extent also true for a family history of cardiovascular diseases, body weight, smoking, use of oral anticonceptives and intake of saturated dietary fats, while alcohol and socio-economical factors showed no relation with lipids or lipoproteins in the young. A favorable relation with daily physical activity and physical fitness was generally observed for triglycerides and high-density lipoprotein cholesterol and appeared not to be gender related. An association between physical fitness and lipids and lipoproteins could be observed only after puberty. Intervention studies on daily physical activity combined with dietary advices documented decreases in total cholesterol and intervention studies on physical fitness showed rises in high-density lipoprotein cholesterol levels (chapter 2.2).

To determine whether physical fitness was related to blood pressure at a

young age, a group of randomly selected 7 to 11 years old schoolchildren was invited and 1,558 children participated in an observational study (response rate 88%). All data collected for both the non- and experimental studies of this thesis, were derived from a longitudinal study in this cohort of schoolchildren, living in Zoetermeer, The Netherlands, during a time period from March 1987 to January 1990. Physical fitness was determined directly by measuring maximal oxygen uptake during a treadmill test. After adjustments for age, skeletal age, height, body weight and sum of skinfolds, physical fitness was not linearly associated with systolic blood pressure. Diastolic blood pressure was inversely related to physical fitness in boys and girls. Lower diastolic blood pressure levels with increasing levels of physical fitness were observed in both boys and girls (chapter 4.1).

The association between hemodynamic factors, blood pressure and physical fitness was studied in 1,081 children, who were randomly drawn from the original study population. Hemodynamic characteristics, including cardiac dimensions and derived measures, were assessed by two-dimensional and M-mode echocardiography. In children with higher levels of systolic blood pressure a larger end-systolic posterior left ventricular wall thickness and a higher cardiac output were found. No relation between diastolic blood pressure and hemodynamic characteristics was observed. Children with higher levels of physical fitness showed larger left atrial dimensions, and increased end-systolic posterior left ventricular wall thickness and left ventricular mass. A higher stroke volume and cardiac output were observed in children with increasing physical fitness. These findings in young prepubertal children may be suggestive of a hyperkinetic state in the early phase of blood pressure elevation. In addition, an increased physical fitness appeared to be related to morphologic and functional changes of the heart already at a young age (chapter 4.2).

Other major cardiovascular risk factors, notably serum cholesterol and lipoproteins, and their relation with physical fitness were examined in the original study population of 1,558 schoolchildren. No relation was observed between total cholesterol, LDL -, HDL -, HDL_2 - or HDL_3 cholesterol and physical fitness. Also, no association could be found between apolipoprotein A-I or B and maximal oxygen consumption. Only in boys apolipoprotein A-II showed an increase with an increasing aerobic capacity. Boys and girls at a relatively high level of physical fitness, i.e., at or above the 90th centile of the VO_2max distribution, showed respectively higher levels of HDL cholesterol and lower levels of LDL cholesterol (chapter 5).

Finally, an experimental study was performed to study the effects of weight loss and increase of exercise on blood pressure in overweight children. These were selected on having a body weight in the upper quarter of the height and age adjusted body weight distribution at two consecutive examinations. 105 children, aged 9-13 years, were randomly assigned to either aerobic exercise two times per week, or a total calorie reduced diet, or a control group. Exercise or weight reduction intervention did not affect diastolic blood pressure, but after 12 weeks the net fall in systolic blood pressure was 3.3 mmHg (90% confidence limits: -6.4, -0.2) in the weight reduction group and 3.1 mmHg (90% confidence limits: -6.2, 0.1) in the exercise group. Children with baseline urinary noradrenaline excretion higher than the median showed a more pronounced decrease in systolic blood pressure in the exercise and the weight reduction group amounting to 5.9 and 3.5 mmHg, respectively. Children with baseline urinary dopamine excretion higher than the median showed a fall in systolic blood pressure in the exercise and the weight reduction group of 7.1 and 3.5 mmHg, respectively. The decrease in blood pressure did not appear to depend on the initial body weight. These observations suggest that exercise and weight reduction may lower systolic blood pressure in overweight children, particularly in those with high urinary noradrenaline and dopamine excretion (chapter 6.2).

In the same randomized trial the effect of body weight reduction and increase of exercise on plasma lipids and lipoproteins was examined. Exercise intervention did not affect plasma lipids or lipoproteins. In the weight reduction group total cholesterol, triglycerides, and apolipoprotein A-II had fallen by 11.5 mg/dl (90% confidence limits: -21.9, -1.1), 18.5 mg/dl (90% confidence limits: -35.8, -1.2), and 5.1 mg/dl (90% confidence limits: -8.9, -1.3), respectively, compared to the control group after 12 weeks of intervention. No changes were observed in urinary electrolyte excretion in both intervention groups. When expressed per total calorie intake, total fat intake decreased significantly in the weight reduction group, compared to the control group. Body weight and sum of four skinfolds were lower in the weight reduction group, compared to the controls. Body weight reduction by total calorie reduced diet in contrast to exercise intervention may lower total cholesterol, triglycerides and apolipoprotein A-II in children with overweight (chapter 6.3).

In the final chapter the conclusions of the studies, both non-experimental and experimental, were discussed in the light of prevention of atherosclerosis at a young age (chapter 7).

SAMENVATTING

De verschillende onderzoeken naar lichamelijke conditie bij kinderen, zoals beschreven in dit proefschrift, betreffen de volgende vragen: (1) is er een relatie tussen lichamelijke conditie en cardiovasculaire risicofactoren, namelijk bloeddruk en serum lipiden en lipoproteinen op jonge leeftijd? (2) wat is het effect van toename van lichamelijke inspanning en afname van lichaamsgewicht op bloeddruk en het lipoproteinen profiel bij kinderen met overgewicht, die neigen tot het ontwikkelen van ongunstige niveaus van cardiovasculaire risicofactoren? (3) en wat zijn vroeg in het leven de mogelijkheden ten aanzien van preventie van toekomstige hart- en vaatziekten?

Het verband tussen bloeddruk en lichamelijke conditie bij kinderen en adolescenten werd nagegaan in gepubliceerde resultaten. Bij kinderen, met name jongens, met een betere lichamelijke conditie werden lagere bloeddruk waarden gevonden. De waargenomen relatie was niet afhankelijk van de leeftijd of de methode waarmee lichamelijke conditie werd gemeten, maar mogelijk wel van het geslacht. Tevens werd het verband nagegaan tussen dagelijkse lichamelijke activiteit en bloeddruk bij jongeren. Onafhankelijk van de meetmethode van dagelijkse lichamelijke activiteit werd geen relatie gevonden met bloeddruk. Resultaten van experimenteel onderzoek, waarin het effect van meerdere factoren waaronder toename van dagelijkse lichamelijke activiteit werd bestudeerd, vertoonden een afname van bloeddruk na een interventie periode van een jaar. Ook werd bij toename van lichamelijke conditie een bloeddruk verlagend effect, voornamelijk diastolisch, gevonden (hoofdstuk 2.1).

Uit recent gepubliceerd onderzoek werd een overzicht van determinanten van serum lipiden en lipoproteinen bij jongeren gepresenteerd, met nadruk op de relatie tussen het lipoproteinen profiel enerzijds en dagelijkse lichamelijke activiteit en lichamelijke conditie anderzijds. Obesitas was ongunstig gerelateerd aan serum lipiden en lipoproteinen. In mindere mate gold dit ook voor een positieve familie anamnese voor hart- en vaatziekten, lichaamsgewicht, roken, het gebruik van orale anticonceptiva en de consumptie van verzadigde vetten. Met alcohol gebruik en socio-economische factoren werden geen verbanden gevonden op jonge leeftijd. Een gunstige relatie met dagelijkse lichamelijke activiteit en lichamelijke conditie werd gevonden voor triglyceriden en HDL cholesterol. Dit verband was onafhankelijk van het geslacht. Het verband tussen serum lipiden en lipoproteinen en lichamelijke conditie werd pas na de puberteit gevonden. Experimenteel onderzoek, waarin toename van dagelijkse lichamelijke activiteit werd gecombineerd met voedingsadviezen, vertoonden een daling in het totaal cholesterol. Experimenteel onderzoek naar het effect van toename van lichamelijke conditie vertoonden een stijging in het HDL cholesterol (hoofdstuk 2.2).

Om het verband te bestuderen tussen lichamelijke conditie en bloeddruk op jonge leeftijd, werd een groep van willekeurig geselecteerde schoolkinderen uitgenodigd en 1.558 kinderen, 7 tot 11 jaar oud, namen deel aan het observationele onderzoek. Alle gegevens, verzameld in het kader van de niet-experimentele en de experimentele onderzoeken in dit proefschrift, zijn afkomstig van een longitudinaal onderzoek van dit cohort Zoetermeerse schoolkinderen gedurende de periode maart 1987 tot januari 1990. Lichamelijke conditie werd bepaald door een directe meting van de maximale O_2 opname tijdens een inspanningstest op een loopband. Na adjustering voor leeftijd, botleeftijd, lengte, lichaamsgewicht en de som van huidplooien, werd geen lineair verband gevonden tussen lichamelijke conditie en de systolische bloeddruk. Diastolische bloeddruk was omgekeerd gerelateerd aan lichamelijke conditie bij jongens en meisjes. Lagere niveaus van diastolische bloeddruk werden gevonden bij jongens en meisjes met hogere niveaus van aerobe conditie (hoofdstuk 4.1).

Het verband tussen hemodynamische factoren, bloeddruk en lichamelijke conditie werd bestudeerd in 1.081 kinderen. Dit was een willekeurige steekproef van de oorspronkelijke onderzoekspopulatie. Hemodynamische karakteristieken, waaronder cardiale dimensies en andere afgeleide metingen, werden bepaald door twee-dimensionale en M-mode echocardiografie. Bij kinderen met een hogere systolische bloeddruk werden een grotere eind-systolische linker ventrikel achterwand dikte en een groter hartminuutvolume gevonden. Met diastolische bloeddruk werd geen relatie gevonden. Kinderen met een betere lichamelijke conditie vertoonden een grotere linker atrium dimensie, een grotere eind-systolische linker ventrikel achterwand dikte en een grotere linker ventrikel massa. Een groter slagvolume en hartminuutvolume werd gevonden bij kinderen met een betere aerobe conditie. Deze resultaten bij jonge prepubertaire kinderen zouden kunnen wijzen op een hyperkinetische toestand in de vroege fase van een verhoogde bloeddruk. Een grotere lichamelijke conditie lijkt al op jonge leeftijd gepaard te gaan met morfologische en functionele veranderingen van het hart (hoofdstuk 4.2).

Andere belangrijke cardiovasculaire risicofactoren, namelijk serum cholesterol en lipoproteinen, en de relatie met lichamelijke conditie werd onderzocht bij 1.558

schoolkinderen. Tussen totaal cholesterol, LDL -, HDL -, HDL_2 -, HDL_3 cholesterol, apolipoproteinen A-I en B en lichamelijke conditie werd geen verband gevonden. Alleen jongens met een toenemende aerobe capaciteit vertoonden een stijging van het apolipoproteine A-II. Jongens en meisjes met een relatief hoog niveau van lichamelijke conditie, d.w.z. groter of gelijk aan de 90ste percentiel van de VO_2max verdeling, vertoonden respectievelijk een hoger HDL cholesterol en een lager LDL cholesterol (hoofdstuk 5).

Tot slot werd een experimenteel onderzoek uitgevoerd om het effect van afname van lichaamsgewicht en toename van lichamelijke inspanning op de bloeddruk te bestuderen bij kinderen met overgewicht. Deze kinderen hadden gedurende twee opeenvolgende metingen een lichaamsgewicht boven de 75ste percentiel van de voor lengte en leeftijd geadjusteerde gewichtsverdeling. 105 kinderen, 9-13 jaar oud, werden willekeurig toegewezen aan een controle groep of twee interventie groepen, die twee maal per week deelnamen aan een programma voor aerobe inspanning, of een totaal calorie gereduceerd dieet volgden. Na 12 weken interventie werd geen effect op de diastolische bloeddruk gevonden, maar de netto afname in systolische bloeddruk was 3,3 mmHg (90% betrouwbaarheids-grenzen: -6,4, -0,2) in de gewichtsreductie groep en 3,1 mmHg (-6,2, 0,1) in de inspanningsgroep. Kinderen met een hogere initiële noradrenaline excretie in de urine toonden een afname in systolische bloeddruk in de inspannings- en gewichtsreductie groep, met respectievelijk 5,9 en 3,5 mmHg. Bij kinderen met een hogere initiële dopamine excretie in de urine werd in de inspanningsgroep een afname van systolisch bloeddruk met 7,1 mmHg en in de gewichtsreductie groep met 3,5 mmHg gevonden. De afname in bloeddruk was niet afhankelijk van het initiële lichaamsgewicht. Deze bevindingen laten zien dat inspanning en gewichtsreductie de systolische bloeddruk bij kinderen met overgewicht kunnen verlagen, met name bij die kinderen met een hoge noradrenaline en dopamine excretie in de urine (hoofdstuk 6.2).

In hetzelfde experiment werd het effect van toename van lichamelijke inspanning en afname van lichaamsgewicht op plasma lipiden en lipoproteinen bestudeerd. Interventie met inspanning had geen effect op plasma lipiden of lipoproteinen. In de gewichtsreductie groep werd een afname van totaal cholesterol met 11,5 mg/dl (-21,9, -1,1), triglyceriden met 18,5 mg/dl (-35,8, -1,2) en apolipoproteine A-II met 5,1 mg/dl (-9,9, -1,3) gevonden, in vergelijking tot de controle groep na 12 weken interventie. In beide interventie groepen werd geen verandering in de excretie van electrolyten gevonden. Totale vet inname, uitgedrukt per totaal calorie inname, nam in vergelijking tot de controle groep significant af in de gewichtsreductie groep. Lichaamsgewicht en de som van vier huidplooien namen af in de gewichtsreductie groep t.o.v. de controles. Afname in lichaamsgewicht door een totaal calorie gereduceerd dieet, i.t.t. interventie met lichamelijke inspanning, kan totaal cholesterol, triglyceriden en apolipoproteine A-II verlagen bij kinderen met overgewicht (hoofdstuk 6.3).

In hoofdstuk 7 worden de conclusies van het observationele en het experimentele onderzoek besproken in het licht van preventie van atherosclerose op jonge leeftijd.

EPILOOG

Graag wil ik iedereen, die op eigen wijze aan het tot stand komen van dit proefschrift heeft bijgedragen, bedanken.

Een epidemiologisch onderzoek kan niet zonder respondenten worden verricht. Met veel respect en bewondering voor hun inzet wil ik alle kinderen en hun ouders, die aan dit onderzoek hebben deelgenomen, heel hartelijk bedanken. Ook alle leerkrachten van de diverse basisscholen uit Zoetermeer, die zich zo belangeloos voor dit onderzoek hebben ingezet, ben ik veel verschuldigd.

Het instituut Epidemiologie en Biostatistiek vormde een plezierige en inspirerende basis van waaruit het onderzoek werd opgezet, uitgevoerd en uitgewerkt. Veel medewerkers zijn bij dit onderzoek direct of indirect betrokken geweest. Een aantal mensen wil ik graag apart noemen.

Allereerst wil ik prof. Bert Hofman, initiator van het onderzoek, bedanken voor zijn stimulerende begeleiding tijdens het onderzoek en later bij de uitwerking van de resultaten. Daarnaast wil ik je, Bert, bedanken voor de mogelijkheden die werden geboden om mij te "scholen tot epidemioloog".

Dr. Rick Grobbee, jou wil ik graag bedanken voor je zeer vakkundige en positieve ondersteuning. Rick, ik heb veel van je geleerd. Mede door jouw creatieve aanwijzingen en snelle oplossingen voor diverse problemen is dit boekje tot stand gekomen.

Prof. Hans Valkenburg, je wijze van begeleiding geven is bijzonder en dwingt veel respect af. Je brede belangstelling, zowel voor het onderzoek als daarbuiten, is voor mij zeer inspirerend geweest. Hans, ik wil je daarvoor graag bedanken.

Dr. Willy-Anne van Stiphout, jij was degene die mij bij aanvang van het onderzoek begeleidde. Met het jou zo kenmerkende en aanstekelijk werkende enthousiasme bracht je me de eerste beginselen van de epidemiologie bij. Door je betrokkenheid en creatieve oplossingen kon zonder kleerscheuren dit onderzoek worden opgezet. Ik wil je daarvoor zeer bedanken.

Een onderzoek van deze omvang is alleen mogelijk door het werk van een groep toegewijde mensen. Hanneke van Meurs, Anneke van der Muil, Ria Rijneveldshoek en Wilma Verbruggen, ik ben jullie dankbaar voor de grote inzet en precisie waarmee jullie het veldwerk in Zoetermeer hebben verricht. Hoe vroeg er ook werd begonnen, of hoe laat er ook werd afgerond, ik kon op jullie rekenen. De studenten van de faculteit Bewegingswetenschappen, Universiteit van Amsterdam,

wil ik bedanken voor het enthousiasme waarmee ze alle inspanningstesten hebben afgenomen. Voor het onderhoud en vervoer van de loopband kon altijd een beroep worden gedaan op Frans Dullemeijer, CRW Erasmus Universiteit, en Theo van der Berg, de "molenaar" uit Zoetermeer. Heidi Mollee, bijgestaan door Marjolein van den Bergh en Mariska de Vette, heeft door haar fantastische inzet het interventie onderzoek tot een groot succes gemaakt.

In het laboratorium van het instituut werden alle bepalingen van serum lipiden en lipoproteinen vakbekwaam verricht door Jeanette Vergeer, Elisabeth van Herpen en René Vermeeren, onder toeziend oog van Ton de Bruyn.

Yolanda Bekker zorgde voor een uitstekende administratieve verwerking. Een goede automatisering is voor een onderzoek onontbeerlijk. Dick Tensen, Marcel Eijgermans, en Robert Rosier, bedankt voor jullie bijdrage!

Ook het secretariaat wil ik bedanken. Met name Ina Bakker voor alle hulp bij het verzorgen van de lay-out van dit proefschrift en Cecilia Kuynders voor de duizend-en-een zaken waarmee ik bij haar terecht kon.

Mijn collega's, de junior-epidemiologen, wil ik ook graag bedanken. Met kamergenootje Annette Bak was het niet alleen goed koffiedrinken! Op onze kamer heerste een fijne sfeer. Arno Hoes en Jan Schouten wil ik graag bedanken voor de vele waardevolle discussies, oppeppende woorden en het delen in onderzoeks-enthousiasme. Hiervoor werd altijd tijd vrij gemaakt ondanks jullie eigen drukke onderzoeksbezigheden. Ik ben blij dat jullie nu paranimfen zijn.

Buiten het instituut Epidemiologie waren ook diverse mensen bij dit proefschrift betrokken. Prof. Wim Saris, afd. Humane Biologie, Rijksuniversiteit Limburg, wil ik graag bedanken voor de inspirerende discussies op het gebied van de inspanningsfysiologie en obesitas. Van Dr. Jan Boogaard heb ik veel geleerd over inspanningstesten. Prof. P. Verdouw wil ik bedanken voor zijn aanvullende opmerkingen over hoofdstuk 4.2. Dr. F. Boomsma verzorgde de catecholaminen bepalingen van het interventie onderzoek. De leden van de leescommissie, prof. J. Hess, prof. J.C. Birkenhäger en prof. W.L. Mosterd, wil ik graag bedanken voor hun commentaar.

Alle familie en vrienden, die met de diverse proefschrift-stadia hebben meegeleefd, bedankt! Mijn ouders wil ik met name graag bedanken voor de vanzelfsprekendheid waarmee ze mij lieten studeren, en voor hun altijd aanwezige belangstelling en ondersteuning.

Lieve Paul, zonder jouw aanwezigheid en support was dit proefschrift er nooit gekomen. Dankjewel.

ABOUT THE AUTHOR

Stella de Man was born on November the 22nd, 1959 in Gouda, The Netherlands. She passed her secondary school exam in 1978 at the "Marnix Gymnasium" in Rotterdam. She studied psychology at the State University of Leiden during one year. From 1979 to 1986 she attended medical school at the Erasmus University in Rotterdam. In 1983 she spent 5 months in a regional hospital in Mukumu, Kenya for clinical experience and to study the prevalence of lues and framboesia in a hospital population (supervisor: Prof.Dr. E. Stolz). A clinical study on the effect of inhalation of hypertonic fluid and histamine on bronchi in children with asthma was performed in 1985 (supervisor: Prof.Dr. K.F. Kerrebijn). During her studies she acted as flutist in the Rotterdam student orchestre "Erasmusica". In May 1986 she obtained her medical degree and started a training as research fellow in Epidemiology at the Department of Epidemiology and Biostatistics, Erasmus University Rotterdam (head: Prof.Dr. H.A. Valkenburg, in 1988 succeeded by prof Prof.Dr. A. Hofman). She married to Paul van der Gaag, economist, in May 1987. Since October 1990, she has started specialist training in Pediatrics at the Academic Sophia Children's Hospital in Rotterdam (head: Prof.Dr. H.K.A. Visser).