ChocHealth for Kids!

The effects of dark chocolate on children's blood pressure

Pilot randomised trial

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Abbreviations

BMI	Body mass index
BP	Blood pressure
CDC	Centres for Disease Control and Prevention
DALY	Disability-adjusted life years
DBP	Diastolic blood pressure
mmHg	Millimetres of mercury
RCT	Randomised controlled trial
SBP	Systolic blood pressure
US	United States

1. Introduction

A persuasive argument can be mounted for systematically effecting lower blood pressure in children. High blood pressure is a significant cause of premature morbidity and mortality. More importantly, blood pressure has a continuous relationship with cardiovascular disease such that many of those within the normotensive range are at greater risk than those with the lowest blood pressure. Even small reductions in average blood pressure have important beneficial effects if the reductions persist over time. Childhood blood pressure is predictive of blood pressure in later life. This presents unique opportunities for population interventions to be implemented in childhood with the goal of reducing blood pressure early on in life.

Screening for hypertension detects only those with extremely elevated blood pressure, missing the wider community who may also benefit from a lowered blood pressure. Administering blood pressure lowering medications to asymptomatic healthy children is unacceptable, as the costs and risks of side effects do not outweigh the anticipated benefits. In addition, the long-term effects of chronic antihypertensive medication use in children are not known.

In contrast, lifestyle interventions to lower blood pressure are appropriate for widespread implementation in the general community. All children will benefit from health-augmenting strategies without significant risks of harm. Unfortunately, most lifestyle modifications are dependent on individual behaviour change, are difficult to achieve, and are rarely sustained. Encouraging regular physical activity and reducing screen time to counter obesity are well-publicised examples.

Dietary modification is one type of lifestyle intervention that could effectively optimise blood pressure. It can occur through reducing intake of a particular food or its contents, such as fats or sodium, or by improving the intake of another, such as fruits and vegetables. There has been a progressive focus on dietary modifications that eliminate individual behavioural factors, such as reducing salt in food products.

Enhancing the intake of an already widely accepted food that also benefits health may be similarly effective. Regular cocoa consumption is increasingly recognised as benefiting health in adults. It is associated with a reduced risk of cardiovascular disease, mediated through lowered blood pressure and improved vascular function, but there have been no trials examining its effects in children. An effective and acceptable school-based program that delivers a small daily dose of dark chocolate could perhaps be an invaluable public health intervention to lower childhood blood pressure and reduce the risks of cardiovascular disease in later life.

However, the many unknowns require substantial preliminary work before such a trial can be mounted. These include the acceptability of such a program to children, their families, schools and the education department, the logistics of intervention delivery and cost-efficiency.

This paper reports the rationale, supporting literature and protocol for a preliminary trial, conducted in late 2010, of daily dark chocolate delivered in the school setting to 10-12 year old children.

2. Background

2.1. Hypertension in adult life

Hypertension is a chronic condition where blood pressure (BP) is persistently elevated. Hypertension in adulthood is one of the most important cardiovascular disease risk factors. Worldwide, 26% of the adult population, or 970 million people, had hypertension in the year 2000.[1] The number of adults with hypertension was predicted to increase to a total of 1.6 billion by the year 2025.[1] In 2007-2008, raised BP affected 9.4%, or 2 million, of all Australians.[2] While it most commonly affected those aged 65 years and above, the condition was not restricted to older adults. Nin Australia, nine percent of those with hypertension, amounting to 180,000 people, were under 45 years of age.[2] Hypertension was the most common individual problem managed by general practitioners in 2005.[3]

Because of its high prevalence, the health and economic costs of hypertension are enormous. In 2004-2005, Australian health care expenditure on cardiovascular diseases was $5.9 billion (11% of total allocated expenditure).[4] While 31% of this cardiovascular disease expenditure went to coronary heart disease and 9% to stroke (both of which are strongly related to hypertension), 60% was spent on other cardiovascular conditions, including hypertension and hypertensive heart disease, amounting to $3.5 billion.[4]

It has been estimated that, in certain age groups, optimising systolic BP (SBP) and diastolic BP (DBP) to 115/75mmHg or below, through a 20/10mmHg SBP/DBP reduction could prevent up to 50% of all vascular mortality.[5] Globally, 7.6 million (13.5%) of all deaths and 92 million (6%) of all disability-adjusted life years (DALYs) per 100,000 population per year in the year 2001 were attributable to high BP.[6] This accounts for 54% of stroke, 47% of ischaemic heart disease, 75% of hypertensive disease and 25% of other cardiovascular diseases worldwide.[6] These rates are similar to those reported by the World Health Organization.[7]

Importantly, it now appears that these health risks are not only associated with clinical levels of hypertension. Across the entire range of BP in adults, including the normal range above 115/75mmHg, morbidity and mortality rise incrementally with BP.[5] Therefore, the role of public health should not only be to screen for and manage hypertension, but to strenuously seek universal interventions that could lower BP across its entire spectrum at the population level. Lowering the average BP of the whole population by a small amount would significantly reduce the total burden of cardiovascular disease.

2.2. Hypertension in childhood

Elevated BP in children is rarely diagnosed, because it is rarely symptomatic. When it is symptomatic, it almost always occurs in a context that requires urgent aetiological investigation and treatment.

The importance of childhood hypertension as an emerging health issue rests chiefly in its strong predictive associations with adult hypertension, which in turn incurs the long-term health risks described above.[8 9] Children with hypertension are 2.5 times more likely to have hypertension as adults.[10] In addition, a meta-analysis of 50 cohort studies indicated that over a five-year period, BP moderately predicted hypertension

(correlation coefficient of 0.43 for SBP and 0.32 for DBP).[11] Similar correlations were reported over 10 years.[11]

Childhood hypertension correlates with early and accelerated development of atherosclerotic lesions in the coronary arteries and the aorta.[12-16] The earliest precursors of cardiovascular disease at a molecular level include alterations in endothelial function in response to various stimuli, such as stress. These changes affect the vascular endothelium, a single layer of cells on the inner surface of all blood vessels that is essential to vascular growth, vasoregulation and vasoprotection. Structural changes in the vessel wall occur as a result, with thickening of the intimal and medial layers, and a reduction in vessel distensibility.[17] Indeed, impaired arterial compliance, increased inflammatory markers and end-organ abnormalities, such as left ventricular hypertrophy and increased carotid arterial intimal-medial thickness, are observed in childhood hypertension.[8 18 19]

Of concern, childhood hypertension is also associated with additional risk factors for metabolic syndrome, including insulin-resistance, truncal obesity, hyperinsulinaemia and dyslipidaemia. In a recent longitudinal study of 342 children aged 11-15 years, childhood BP was found to predict early adulthood dyslipidaemia, independently of body mass index (BMI).[9]

2.3. Definitions of hypertension in childhood

Classification of BP in youth is based on the normative distribution of BP measurements in healthy children and adolescents according to their gender, age and height. Therefore, current definitions are empirical and somewhat arbitrary, though nonetheless strongly implicated in later adult hypertension. Of the various definitions available, the most widely used is the 2004 US-based 4th Report from the National High Blood Pressure Education Program Working Group on Children and Adolescents.[8]

Under their definition, normal measurements are below the 90th percentile. Hypertension is present when average SBP and/or DBP measurements are ≥95th percentile for gender, age and height, on three or more occasions. Hypertension can then be further classified as Stage 1 (BP levels ranging from the 95th percentile to 5mmHg above the 99th percentile) and the more severe Stage 2 (BP levels that are more than 5mmHg above the 99th percentile). When average BP is at or above the 90th percentile but below the 95th percentile, the child or adolescent is considered to be pre-hypertensive.

As well as by severity, hypertension can be differentiated by aetiology.[19] Primary, or essential, hypertension occurs in the absence of a pathological cause, although it is associated with obesity, insulin resistance, central distribution of adiposity and lifestyle factors such as sedentary activities. Secondary hypertension results from a medical disorder such as renal disease, vascular abnormalities or endocrinopathy.

2.4. Prevalence

Reported prevalence of asymptomatic pre-hypertension and hypertension in school-aged children varies from 1-18%. A US school-based study of 5,102 students, aged 10-19 years from eight public schools, observed hypertension in 4.5% of their study population.[20] A Turkish school-based study of 1,346 adolescents aged 15-18 years reported hypertension in 3.5%.[21] An Italian outpatient study reported pre-hypertension in 17.7% of 447 obese children and 1.5% of 131 normal-weight children

aged 6-16 years.[22] A recent Melbourne study from the Centre for Community Child Health with 256 10-year-old children identified a prevalence of 10.2% for pre-hypertension, 1.6% for Stage 1 hypertension and 0.4% for Stage 2 hypertension.[23] Differences in rates of high BP probably reflect the labile nature of blood pressure (easily affected by activity and emotions) and the difficulties in accurately measuring BP in children.

Primary hypertension accounts for 33-45% of children with hypertension and is more prevalent in older children and adolescents.[24 25] It is an emerging health concern as its prevalence is rising in association with the current epidemic of childhood obesity,[9 19 26-28] and it is becoming a more common cause of hypertension in childhood.[20 29]

Childhood and adolescent obesity has increased three- to six-fold over the past three decades.[30 31] US data from 2007-2008 indicated 29% of 2-19 year olds are overweight,[32] increased from 12% in 1999-2002.[33] In 2007-2008, 25% of Australian children aged 5-17 years were overweight or obese.[2]

The strong and incremental association between childhood BP and BMI exists across the entire range from normal weight to overweight,[20 34] with overweight children being three times more likely to have elevated BP.[29] Of significant concern, the effects of childhood hypertension and obesity are additive, and synergistically increase the long-term health risks of cardiovascular disease in later life.[9 29]

While the presence of an obesity epidemic is alarming, high BP and its health risks also affect the 75%of Australian children who are neither overweight nor obese.[2] Only 20% of children with pre-hypertension or hypertension are obese, and around 45% of them are of normal weight.[35] Any effective lifestyle intervention to lower BP will need to include the larger population of lower-risk, normal-weight children.

2.5. Intervening to reduce blood pressure

The morbidity and mortality associated with hypertension should be preventable through early interventions that effectively reduce BP. Any population-wide reduction in BP should result in a proportional decrease in cardiovascular risk at a population level, because the association between high BP and cardiovascular risk is direct and continuous.[36] The magnitude of BP reduction appears to be a pivotal factor in achieving cardiovascular health benefits.[36-38]

Using pharmacological-based treatment in hypertensive adults to reduce SBP by 5-8mmHg and DBP by 2-5mmHg significantly reduced the risk of stroke (28-38%), major cardiovascular events (18-22%) and all-cause mortality (11-12%).[39] A systematic review of 105 randomised controlled trials (RCTs) from 1998-2003 found that lifestyle interventions, such as improved diet and exercise and restriction of alcohol and salt intake, can similarly reduce average BP in hypertensive adults by 2-6mmHg.[40]

In general, a 10mmHg reduction in SBP is expected to decrease the risk of a major cardiovascular event by 20-25%.[41 42] However, even small reductions in BP would have significant public health benefits if experienced by the whole population, as large absolute numbers of premature mortality and morbidity would be avoided. It has been reported that a 2mmHg lower usual SBP would result in a 10% and 7% lower mortality from stroke and ischaemic heart disease, respectively, in middle age.[5] A Cochrane review of modest salt reduction (~5g/day for four or more weeks) on BP in normotensive adults showed a mean decrease in SBP/DBP by 2/1mmHg.[43] It was estimated that this immediately decreased stroke and ischaemic heart disease

deaths by 14% and 9% respectively in hypertensive persons, and by 6% and 4% respectively in normotensive persons.[44]

Furthermore, the effects of early lifestyle interventions may be amplified with increasing age. In a study involving 2,192 children aged 9-15 years in Estonia and Denmark, the association of breastfeeding and lowered mean SBP (–1.7mmHg; 95 per cent CI -3.0 to -0.5) was greater in 15 year olds (mean SBP –2.4mmHg; 95 per cent CI -4.0 to -0.8) than in 9 year olds (mean SBP –1.4mmHg; 95 per cent CI -3.3 to 0.5).[45] Similarly, the worldwide INTERSALT study found an association between mean population salt intake and the gradient of normal age-related BP increase over 30 years (from 25 years old to 55 years old). A lowered sodium intake by 6g/day (100mmol/day) – identified by lowered sodium excretion – decreased the 30-year difference in SBP/DBP by 10-11/6mmHg.[42 46]

Efforts that could successfully maintain lower childhood BP at the population level would reduce the risk of developing pre-hypertension, hypertension and associated disease in later life.

2.6. Prevention and treatment of child hypertension

There are two potential public health approaches to the prevention of childhood hypertension and pre-hypertension at a population level:

- screening followed by targeted intervention, and/or
- universal intervention.

Screening programs followed by targeted intervention pose a number of challenges for elevated BP in children. BP screening in children is unreliable, inaccurate and non-reproducible as measurements are often affected by natural fluctuations from activity and emotions, which are not easily managed in children. This is seen in the range of prevalence rates reported, and the decrease in rates on subsequent screening sessions.[27] The optimal BP levels for children, given the arbitrary nature of the definitions of hypertension, are not known. There is no evidence to assist in the definition of the ideal target population that, when identified and treated, will lead to particularly improved health outcomes.[47] The treatment objectives of clinical hypertension remain opinion-based[48] and there is no information available regarding the cost-effectiveness of screening for elevated BP.[49] Childhood raised BP does not satisfy the widely accepted criteria for screening described by Wilson and Jungner.[50]

Given the continuous association between BP and BP-related disease, universal programs are likely to be more achievable and more relevant. Interventions could potentially be either medication-based or lifestyle-based.

In children, pharmacological treatment is currently recommended only for clinical hypertension with inadequate response to lifestyle modifications, evidence of end-organ abnormalities, or hypertension secondary to an underlying disorder.[8] Antihypertensive agents would not be considered acceptable for use in children with asymptomatic high-normal BP, as there is an unjustifiable and unnecessary risk of exposure to side effects and their use would likely need to be long-term. Therefore, it is not surprising that no RCTs in healthy children have investigated long-term effects of lowering BP by medications. The effects of chronic use of antihypertensive medications on a child's growth and future development are not clear. Trials examining these effects would involve high costs and long duration and are unlikely to be performed. In addition, the expected risks do not outweigh any anticipated benefits. There remains limited data regarding efficacy, safety, pharmacokinetics and pharmacodynamics of specific antihypertensive agents when used in children.[48]

Lifestyle strategies are safer and may be less intrusive. Theoretically, all children would benefit regardless of their BP, as the recommendations promote general health and lower BP. Lifestyle modifications include weight reduction, dietary adjustments (e.g. Dietary Approach to Stop Hypertension (DASH) diet,[51] sodium reduction[52]), regular physical activity, decreasing cigarette smoke exposure and managing sleep-disordered breathing.[8 19 53]

Unfortunately, lifestyle changes rely on cognitive and behavioural adaptations by individuals and are a challenge to achieve. In adult studies, weight loss is effective in decreasing BP[54-56], but weight loss is difficult to sustain. In the Trials of Hypertension Prevention (Phase II), more than 60% of the adult participants who had significant weight loss (4.5kg or more) at six months were unable to maintain their weight at 36 months.[57] Similarly, dietary modifications and other comprehensive lifestyle interventions are effective in adults,[55 58] but may be difficult to implement because of poor adherence.

The long-term benefits of short and medium-term lifestyle interventions on BP are inconclusive. The Trials of Hypertension Prevention studies reported beneficial effects on BP at seven years despite loss of other intervention effecs[56], and suggested weight loss in overweight adults, even if not sustained beyond 6 months, is associated with improved blood pressure long-term.[57] However, more recently a meta-analysis of adult studies suggested that, regardless of maintained weight loss, BP reverts back to higher levels after 2-3 years.[54] This may be related to unsustained lifestyle changes, age-related processes, or the effect of other not yet recognised lifestyle aspects.

There is less research investigating the feasibility and outcomes of lifestyle interventions for BP in children. The Child and Adolescent Trial for Cardiovascular Health (CATCH) study investigated the effects of a three-year multi-component program involving school environmental changes, classroom curriculum and, in some schools, family intervention. While it modified school lunch and school physical education programs, as well as student fat intake and physical activity behaviours, there was no change between intervention and control groups in BP, body size or cholesterol measures at the end of intervention.[59] At three years after completion of the program, there was a persistence of self-reported dietary and physical activity behaviours, but again no difference in BP, body size or cholesterol measures.[60]

To date, there are no easily sustainable lifestyle programs for lowering BP in youth. The recent move to reduce the standard sodium content of core and processed foods throughout Australia and internationally offers some promise,[61-64] although some believe individual choice is breached in the process.[65] Another approach may be to enhance appropriate intake of already widely accepted foods that have beneficial effects, specifically functional foods.

Functional foods enhance physiological health above basic nutritional needs. Below, we explore the potential role for dark chocolate as a functional food and the rationale for a trial of dark chocolate to lower BP in children and reduce cardiovascular burden in later years. Specifically, whether a school-based program delivering a daily small dose of dark chocolate may be effective and acceptable.

2.7. Health effects of cocoa

There is epidemiological and controlled trial evidence for health benefits with regular cocoa consumption.[66-79] As no studies have been performed investigating cocoa and health outcomes in children, the evidence discussed below comes from adult studies or laboratory research.

Observational studies have linked ingestion of cocoa-containing foods to lower cardiovascular mortality. Most recently, a cohort study of 19,357 healthy German adults followed for eight years found an intake of 6g of chocolate/day was associated with a 39% decreased risk of myocardial infarction and stroke.[67] In 2009, a prospective cohort study of 1,169 adults, recruited after a first acute myocardial infarction and followed for eight years, found a cardiovascular mortality of 6% in those who usually consumed any type of chocolate two or more times a week, compared to 14.5% in those who never ate chocolate.[68] The Zutphen Elderly Study of men free of coronary heart disease found those who had a cocoa intake of 3-6g/day (approximately 10g of dark chocolate) had a 45-50% lower risk of cardiovascular and all-cause mortality after 15 years compared to non-consumers.[73] Cross-sectional analysis also found a SBP/DBP difference of 3.7/2.1mmHg between the two groups.

Cocoa consumption has been shown in intervention studies to have BP-lowering effects. An up–to-date meta-analysis of 10 RCTs comprising 297 healthy, prehypertensive and Stage 1 hypertensive adults regularly ingesting cocoa products for two weeks or more, found a decrease in mean SBP/DBP of 4.5mmHg/2.5mmHg.[80]

Other beneficial effects of cocoa described include improved endothelial function,[77 78 81 82] decreased insulin resistance,[69 76] improved vascular[70] and platelet function,[81 83-87] and antioxidant and immunomodulatory effects[88] making it a potential functional food.

The mechanism and health effects of dark chocolate are attributed to polyphenols found in cocoa.[88-91] Studies in vitro and in vivo have shown that flavanols, a type of polyphenol, up-regulate nitric oxide synthethase[92] and increase bioactive nitric oxide,[71 93] enhancing effects such as vasodilation[76 78 82] and insulin sensitivity.[75] Antioxidant effects[88] are evidenced with delayed oxidation of low-density lipoproteins[94 95] and reduced production of reactive oxygen radicals.[79] Further, ADP-stimulated platelet activation is suppressed with cocoa consumption, protecting against thrombosis by decreasing haemostasis, platelet aggregation and adhesion.[87]

Unfortunately the most effective dose and form of cocoa-containing food product is unclear.[66] Most studies utilise dark chocolate as intervention as it has a higher cocoa, and therefore higher polyphenol, content.

Evidence for acute short-term effects are seen with consumption of about 170mg of flavanols, as a 100mL cocoa drink[82] or as 40g of commercial 74% dark chocolate.[81] Within two hours of ingestion, bioactive nitric oxide levels in plasma is tripled and flow-mediated vasodilation is improved in adults with cardiovascular risk (including 27% with arterial hypertension).[82] In a different study, improved flow-mediated dilatation, platelet function and plasma antioxidant status was seen within two hours in healthy smokers.[81]

Variable doses and duration for longer-term effects have been investigated. In a RCT involving 44 middle-aged (56-73 years) adults with untreated pre-hypertension or Stage 1 hypertension, low-dose daily consumption of cocoa as 6.3g of dark chocolate (30mg polyphenol) for 18 weeks, compared to control (polyphenol-free white chocolate), effectively reduced mean SBP/DBP by 2.9mmHg/1.9mmHg with no associated changes in body weight or lipid profile.[71] A meta-analysis of other intervention studies using higher doses of chocolate (up to 100g per day, containing 200-500mg of flavanols) for shorter duration (two weeks) in normotensive, pre-hypertensive and Stage 1 hypertensive adults reported greater reductions in mean SBP/DBP (4.7 mmHg/ 2.8 mmHg).[96]

However, studies with no effect on BP have also been reported[77 78 97 98] even when improvement in endothelial function was demonstrated.[77 78] These inconsistent

results are difficult to explain as the trials' designs are heterogeneous. BP effects may have been missed because of factors such as smaller sample population, shorter intervention duration, or intervention in normotensive adults. It has also been suggested that factors other than flavanol dose, such as the form of cocoa product, may be important in effecting change in BP.[66]

2.8. Potential adverse effects

Before advocating regular chocolate consumption for health benefits, potential adverse effects must be considered. Chocolate is energy dense and has a high fat and sugar content, leading to concerns that regular intake will lead to detrimental weight gain or dyslipidaemia. However, Taubert et al.[71] reported no difference in body weight in their 18-week study using 6g of dark or white chocolate daily. In a different study, daily consumption of 41g commercial dark chocolate, 60g almond or both for six weeks also did not result in weight gain or changes in serum cholesterol concentrations in 49 healthy women.[74]

It is suggested that the effects of cocoa may predominate over any unfavourable effects of fats (cocoa butter in dark chocolate) and a number of studies have reported an increase in high-density lipoproteins, a decrease in triglycerides, or a decrease in total and/or low-density lipoproteins (LDL) with chocolate consumption.[89] This may be due to the combination of stearic acid (33% of cocoa butter) having no effect on cholesterol profile, and the antioxidant effects of cocoa inhibiting oxidation of LDL.

Another potential negative aspect of chocolate consumption is that it is usually sweetened with sugar. Frequent and regular consumption of foods high in sugars are associated with dental caries, dyslipidaemia, obesity, bone loss and fractures, and poor diet quality.[99] Most of this research is based on sugar-sweetened beverages. Significant risk for dental caries is present if sweet snacks are consumed more than five times a day in between regular meals.[100] However, other factors also influence the occurrence of caries such as oral hygiene, fluoride supplements and fluoride toothpaste. Adverse associations can be minimised by limiting sugar to less than 8-10% of total energy intake.[101 102]

2.9. Acceptability

Per capita, Australians consume five kilograms of chocolate each year, accounting for about 60 percent of total confectionary industry sales.[103] On average, Australian children aged 8-11 years consume between 8-12g of chocolate and 6-8g of sugar confectionary per day.[104 105] There is no evidence on their preferred type of chocolate, but anecdotally, children prefer milk chocolate. Indeed, in the longitudinal observational study of German adults and their chocolate consumption, of those who reported chocolate consumption in their 24 hour dietary recall, 57% reported intake of milk chocolate, 24% dark and 2% white (17% did not specify type).[67]

Milk chocolate and sugar confectionary are recognised for their nutrition-poor ingredients such as high sugar and processed fats. Healthier options are being sought as potential additions to children's lunch boxes, and the potential benefits offered by dark chocolate may make it highly favourable and appropriate, although recommended quantity needs to be emphasised.

3. Aims and hypotheses

Based on the rationale reported above, in late 2010, we conducted a preliminary trial of the possible benefits and harms of daily dark chocolate delivered to older primary school children (aged approximately 10-12 years) in Melbourne, Australia. Because such a trial has not been previously attempted, the feasibility and acceptability of daily dark chocolate in this age group were also not known, nor those of the trial's logistics and methods. Therefore, these aspects were equally on trial in the project reported below.

3.1. Aims

In a pilot randomised controlled trial, we aimed to:

- Determine whether a school-based program promoting daily intake of seven grams of dark chocolate on school days over seven weeks by healthy Grades 5 and 6 children is an acceptable and feasible intervention in Melbourne metropolitan primary schools for reducing blood pressure in children
- Identify the most acceptable methods of intervention delivery
- Document any barriers in the implementation and uptake of such a program
- Establish the feasibility of measuring anthropometry (height, weight, waist circumference), percentage body fat by bioelectrical impedance analysis, blood pressure, and endovascular function by pulse wave analysis using SphygmoCor in all in-age children in a school setting
- Estimate variability (standard deviation of change over time) in blood pressure in children, to inform sample size estimates for a larger trial should it proceed
- Conduct preliminary comparisons between the intervention and control groups on key outcomes, to inform sample size estimates for a larger trial should it proceed.

3.2. Hypotheses

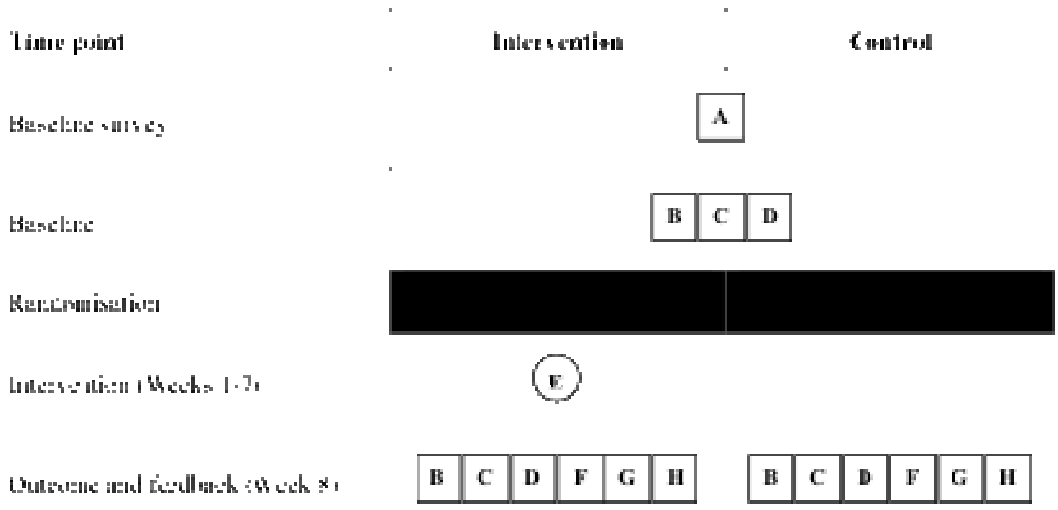
- We hypothesised that:
- The intervention would be feasible and acceptable for 10-12 year old children, their parents and their schools
- At two months post-randomisation (after about seven weeks of regular daily dark chocolate consumption), the intervention group, when compared with the control group, would show:
    - trends towards a lower mean systolic and diastolic blood pressure (primary outcome),
    - no difference in mean height, weight, BMI, body fat, waist circumference and self-reported health-related quality of life,[106] self-perception[107] and body image[108] (secondary outcomes).

4. Research plan

4.1. Design

ChocHealth for Kids! is a school-based pilot randomised controlled trial involving Grade 5 and 6 students of recruited schools. Figure 1 shows the components of the trial.

Figure 1 - Graphical depiction of *ChocHealth for Kids!* pilot randomised controlled trial



Legend:

A	Parent invitation pack (information statement, written consent form and survey) distributed to parents of all Grades 5 and 6 students attending participating schools. The survey asked about family demographics, socioeconomic details, their child's food intake and lifestyle habits, medical history and health-related quality of life.[109]
B	Blood pressure: All students participating will have their blood pressure measured using an automated sphygmomanometer at baseline and at outcome.
C	Pediatric Quality of Life Inventory,[106] Collins Body Figure Scale,[108] and modified Harter's self-perception profile[107]: This survey will be completed by all students at baseline and at outcome.
D	Anthropometric measurements: All participating students will have their weight, height, waist circumference, and body fat measured at baseline and at outcome.
E	Intervention: Seven grams of dark chocolate is delivered to each participating student in intervention classes via their class teacher, during lunchtime every school day, for seven weeks.
F	Pulse wave analysis[110]: All participating students will have their endothelial function assessed by applanation tonometry at outcome.

G	Student evaluation. Follow up survey completed by students during outcome assessments.
H	Teacher evaluation. Follow up survey directly delivered to participating teachers after completion of intervention. It will include questions to identify successful and challenging aspects of the study to evaluate acceptability and feasibility.

4.2. School recruitment

For the primary aim of ascertaining feasibility and acceptability, a convenience sample of several independent primary schools in metropolitan Melbourne, Australia, based on proximity to the research office (The Centre for Community Child Health, Royal Children's Hospital Melbourne, Australia) and size of Grades 5 and 6 student population, was approached and invited to participate. Principals were initially invited by phone to participate in the study. A brief project outline in writing was then provided to the school for all staff to consider. The first two schools to agree were recruited and a key contact person for liaison for the duration of the trial was then identified.

A memorandum of understanding was signed between the Centre for Community Child Health and participating schools, asking schools to agree to:

- a single group interview with the teachers to obtain their views about how best to administer the intervention
- provide space to conduct initial and outcome measurements
- distribute the intervention chocolate according to agreed instructions between individual teachers and the research team.

We met with all the Grades 5 and 6 teachers at each school for approximately 30 minutes to describe the expected time commitments, recruitment, measurement and intervention processes, and answered any questions they had prior to commencement of the trial.

4.3. Participant recruitment

We approached all students in Grades 5 and 6 in participating schools. We first publicised the trial in the form of school newsletter inserts and take-home postcards during the two weeks leading up to recruitment to raise general awareness. We then arranged to meet with each of the classes, for approximately 15 minutes each, to explain the study and address any questions students may have prior to recruitment.

All Grades 5 and 6 students were provided an invitation pack to take home to their parents, containing a letter of invitation, plain language information, consent form, sealable envelope and a baseline demographic questionnaire for parents to complete.

The baseline demographic questionnaire included details about the child's age, gender, general health, any chronic illnesses, food allergies, medication history, current diet and frequency of chocolate consumption, physical activity, family history and exposure to cigarette smoke. Socio-demographic data (parental employment, qualifications, income) were also collected.

Parents who declined for their child to participate in the trial could consent for their child to have daily dark chocolate along with heir classmates (if their class was later randomised to intervention arm), or could indicate for their child not to be involved in any aspect of the trial (no chocolate).

Parents were asked to return the completed questionnaire and consent form in the provided envelope, sealed, to their child's teacher within two weeks. Their teacher recorded who had responded and sent home a reminder pack, containing all the contents of the invitation pack, with any student who did not return their survey in 10 days. Returned envelopes were stored in supplied secure boxes in each classroom until a member of the research team collected them prior to baseline measurements.

4.4. Eligibility

All students who returned written consent and the completed parent questionnaire were eligible for participation in the study.

4.5. Exclusion criteria

The parent baseline questionnaire screened for exclusion criteria, with parents then contacted to discuss details and clarify their child's past medical history. Students were excluded from the study if they**:**

- Are concurrently undergoing treatment for hypertension – this could unpredictably alter the effects of dark chocolate.
- Have a serious allergy, such as anaphylaxis, to nuts or diary and carry adrenaline autoinjector(s) – although we used dark chocolate that did not contain nuts, it was processed on factory machines that also process chocolate with nuts. Most dark chocolate also contain small amounts of milk solids.
- Have a significant developmental or health condition that limits their participation.
- Were in a class with an overall response rate less than 65%. This was an arbitrary decision due to our feeling that if less than two-thirds of a class was participating, intervention delivery was likely to be compromised.

4.6. Randomisation

After baseline measurements (see below), students were clustered by class and randomly allocated to either the dark chocolate (intervention) arm or no chocolate (control) arm. An independent statistician from The Centre for Epidemiology and Biostatistics Unit at The Royal Children's Hospital Melbourne created the computerised cluster (class) randomisation sequence with clusters stratified by school and year level. The sequence enabled a minimum ratio of one intervention class to one control class, up to a maximum ratio of two intervention classes for one control class in each year level, at each school. This enabled us to test intervention delivery processes to more children than a 1:1 ratio, while still providing a comparison group and allowing feasibility tests of the control condition.

Researchers involved in baseline and outcome assessments remain blinded to class allocation throughout the study. However, it was not possible to keep parents, participants or schoolteachers blinded throughout the study with the commencement of intervention. All participants and families were asked not to change their regular diet and lifestyle.

4.7. Intervention

The commercial dark chocolate used as intervention in this study was chosen on the basis of its availability, palatability and antioxidant content. Epicatechin and catechin (both monomer types of flavanols) appear to be the major mediator of cocoa health effects.[111] We first arranged for two commercially available brands of dark chocolate to be analysed at a laboratory (Southern Cross Plant Science, formerly Centre for Phytochemistry and Pharmacology, Southern Cross University) independent of the two companies. The chocolates were analysed by high-performance liquid chromatography using ultraviolet-visible photodiode array, with the instrument calibrated for caffeine and catechin. All catechins were calculated against the catechin standard and then extrapolated using pre-defined correction factors for the respective catechin derivative. Extraction of these chemicals from the chocolate matrix was achieved sequentially with the chocolate specimen in methanol, facilitated by sonication. Heating was avoided to minimise degradation of phytochemicals. The sequential extracts were then analysed individually and the values from each extract summed to provide the total amount of epicatechin, catechin, caffeine and theobromine.

Haigh's Chocolates[112] was chosen for its higher epicatechin/catechin content. An isolated batch was used in this study.

Students in classes randomised to the intervention (chocolate) arm received seven grams of dark chocolate from their teacher every school day over School Term 4 (about seven weeks - this period was chosen to fit into a single school term and to be sufficiently long to study the feasibility of prolonged administration). This took place immediately before the students ate their lunch to maximise capture and minimise risks of dental caries. Children in control arm classes did not receive chocolate, and continued their school days as usual. This is because there is no appropriate polyphenol-free chocolate with any nutritional benefits.

On a weekly basis, an unblinded research assistant packed one week's supply of dark chocolate for each intervention class and delivered this to participating schools. These weekly visits also provided the opportunity to trouble-shoot and fine-tune the delivery of the program as needed.

Each intervention class teacher received five multi-compartment plastic food-safe trays labelled Monday to Friday every week. Each participating student in intervention classes was allocated the same named compartment in each of their class's five trays. Each compartment contained seven grams of individually packed dark chocolate in food-safe zip-lock bags.

- To monitor compliance, the unblinded research assistant recorded any compartments that were not emptied and the reason (where available) when they collected the plastic boxes each week.

4.8. Measurements and procedures

At baseline and at follow-up (immediately after the completion of seven weeks of intervention), all students underwent physical measurements. These were conducted at the schools on a school day by a small group of trained researchers, working through each class in turn. Students were measured in groups of five, during 20-30 minutes away from their usual class in a separate and private area provided by the school. During this period, students were called away one at a time to have their weight, body fat, waist circumference and height measured privately in a screened area. All students were provided with a record of their physical measurements at the end of the session, unless they specifically requested not to receive it.

Baseline measurements were taken prior to randomisation and intervention delivery. Outcomes were collected in December 2010, using the same procedures and measures as at baseline, undertaken by assessors blind to group allocation. In addition, participating children:

- completed a short questionnaire to provide their feedback and suggestions about the trial and its methods
- answered a short self-report questionnaire on recent chocolate consumption (same questions as in baseline questionnaire)

Measurement training

All researchers undertaking the physical measurements were trained by researchers at The Centre for Community Child Health experienced in conducting similar measurements in community research projects. Staff was trained in a single two-hour session where the method for each measurement was demonstrated and repeatedly practiced by each researcher to ensure accuracy, reliability and competency.

Primary outcomes

There were two primary outcomes for this trial. Acceptability and feasibility was evaluated through overall participation rate, intervention adherence, retention rate and written feedback from students and teachers. Students reported their individual experience being part of the study and perceptions of dark chocolate in a follow-up questionnaire at outcome. Each participating teacher completed a feedback questionnaire reporting their trial experiences, any barriers encountered, and any suggested improvements for a larger, definitive trial.

From the pilot data, mean systolic and diastolic blood pressure in the intervention group compared to the control group was the primary outcome. Blood pressure was measured, at each time point, after the student was seated for approximately three minutes, whilst completing a written questionnaire. Blood pressure was taken on the non-dominant arm, at the level of the heart, with a correctly sized cuff attached to an automated sphygmomanometer.

Where the mean SBP is above the 90th normative centile for the student's age, gender and height,[8] suggesting possible pre-hypertension or stage 1 hypertension, a letter was sent home with the student to their parents recommending the student's blood pressure to be rechecked by their general practitioner at their next visit. If stage 2 hypertension was detected, we also contacted the student's parent by telephone to recommend a general practitioner review within the next two weeks. In both instances, we also provided a research contact number in the event the parents had further questions.

Secondary outcomes

Our other outcome measures included height, weight, BMI, body fat, waist circumference and self-reported health-related quality of life,[106] self-perception[107] and body image.[108] These were also obtained at baseline and at outcome. Details for obtaining these include:

- Anthropometry – Students were asked to remove their shoes, socks and heavy outer garments for these assessments. Each student was *weighed* using regularly calibrated digital scales accurate to the nearest 50g, and had their *height* measured using portable rigid Invicta stadiometers (widely used in Australian field studies of child obesity). *Body mass index* (BMI, kg/m^2) was calculated and transformed to current Centers for Disease Control and Prevention (CDC) Growth Chart Z-scores that adjust for skew, age and sex.[113] *Waist circumference* was measured to the nearest 0.1cm with a Lufkin W606PM anthropometric steel tape using standard procedures. We recorded the mean of two heights and girths; if they differed by >0.5 cm (height) or >1.0 cm (girth), we recorded a third measurement. Anthropometry was used to explore if and how our intervention altered body habitus compared to control.
- Multiple frequency bioelectrical impedance analysis (BIA) was performed using a portable body composition analyser/scale. BIA is a low-cost and convenient measure of the impedance of the body tissues to the flow of a small electrical current. Height^2/impedance is proportional to total body water, from which fat mass and percentage body fat can be estimated using a child-specific population equation. This procedure is non-invasive, safe and well tolerated in large-scale epidemiological studies of children's body composition. It would be important to assess for any significant effects on body fat composition with our intervention.
- Health-related quality of life and body image – The participants completed the 23-item *PEDS QL 4.0 Child Self-Report*,[106] a validated measure of child quality of life, the Collins Body Figure Scale[108] and the modified Harter's self-perception profile.[107] These were completed by all students while seated independently on separate tables. They allowed us to determine any benefits or harms arising from the intervention, and allowed the students to sit quietly for 10 minutes for their blood pressure measurement.

At follow up, we had aimed to assess endothelial function by applanation tonometry using Pulse Wave Analysis (SphymoCor Px/P Pulse Wave Analysis System, AtCor Medical, Sydney, Australia) after blood pressure was measured. Pulse Wave Analysis is a non-invasive assessment of arterial stiffness and, indirectly, endothelial dysfunction.[110 114] Due to time constraints, Pulse Wave Analysis was not feasible during this pilot study.

4.9. Sample size

As this was a pilot trial, the aim of the trial centred on evidence of feasibility over efficacy. Nonetheless, formal statistical analysis was undertaken to determine standard variability of change of physical measurements, in particular blood pressure, over time. This will inform accurate sample size estimation for a larger trial.

Two schools took part in the study, each with approximately three Grade 5 and three Grade 6 classes of approximately 23 students in each class. Working within different

classes and schools provided good information about the range of reactions and challenges likely to be encountered for any definitive trial.

About 280 students and 12 teachers were approached from the two schools. It was expected that at least 75% of families will consent to participate in the study, and less than 5% will be excluded according to our defined criteria. Although students were recruited at the school class level, we expected clustering effect to be very small once adjusted for individual body mass index, since blood pressure is highly heritable and individual. We did not expect it to be influenced by their class allocation.

4.10. Statistical analysis

A statistician from The Royal Children's Hospital Melbourne's Clinical Epidemiology and Biostatistics Unit led the study results' analysis. The characteristics of the students randomised to the intervention arm was described separately and compared to students allocated to the control arm. This included a summary of the students' sociodemographics, lifestyle, and family history. Acceptability and feasibility was described qualitatively through response rates, intervention adherence, retention rate and feedback from students and teachers.

Preliminary trial outcomes between intervention and control groups were analysed and compared applying the intention-to-treat principle. Quantitative results will be described using means, mean differences, standard deviations, ranges, confidence interval and p-value. Linear regressions will be conducted to compare the two groups. Adjusted regression will include confounders chosen *a priori* (age, gender, parent education) and baseline values for each particular outcome measure. Statistical significance will be considered at the 5% level.

5. Outcomes and significance

Blood pressure has an alarmingly continuous association with the development of cardiovascular diseases, and is the top contributor to global mortality. There is an urgent need to identify primary prevention strategies that are both effective and acceptable to the general population, especially at a young age, as the potential for long-term health benefits is enormous.

This pilot trial explored the feasibility and acceptability of a school-based intervention delivering a common cocoa-containing food product that is increasingly recognised to lower blood pressure and enhance endovascular function. Our findings will inform the processes of a larger efficacy intervention trial should it proceed, including the management of any barriers and difficulties.

This trial also provided original contributions towards the knowledge surrounding dark chocolate in children – its appeal, any immediate health benefits from short-term regular consumption, as well as any adverse outcomes.

The trial's results have been reported[115] and are available at Archives of Disease in Childhood (http://adc.bmj.com/content/97/7/637.abstract?etoc).

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