



Design and strategies used for recruitment and retention in a double blind randomized controlled trial investigating the effects of soluble corn fiber on bone indices in pre-adolescent children (PREBONE-Kids study) in Malaysia

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ABSTRACT

Background: Recruitment and retention in longitudinal nutrition intervention studies among children is challenging and scarcely reported. This paper describes the strategies and lessons learned from a 1-year randomized double-blind placebo-controlled trial among pre-adolescent children on the effects of soluble corn fiber (SCF) on bone indices (PREBONE-Kids).

Methods: Participants (9–11 years old) were recruited and randomized into 4 treatment groups (600 mg calcium, 12 g SCF, 12 g SCF plus 600 mg calcium and placebo). Interventions were consumed as a fruit-flavored powdered drink for 1-year. School-based recruitment was effective due to support on study benefits from parents and teachers, peer influence and a 2-weeks study run-in for participants to assess their readiness to commit to the study protocol. Retention strategies focused on building rapport through school-based fun activities, WhatsApp messaging, providing health screening and travel reimbursements for study measurements. Compliance was enhanced by providing direct on-site school feeding and monthly non-cash rewards. Choice of 2 flavors for the intervention drinks were provided to overcome taste fatigue. Satisfaction level on the manner in which the study was conducted was obtained from a voluntary sub-set of participants.

Results: The study successfully enrolled 243 participants within 6 months and retained 82.7% of the participants at the end of 1 year, yielding a drop-out rate of 17.3%. Compliance to the intervention drink was 85% at the start and remained at 78.7% at the end of 1 year. More than 95% of the participants provided good feedback on intervention drinks, rapport building activities, communication and overall study conduct.

Conclusion: Successful strategies focused on study benefits, rapport building, frequent communication using social media and non-cash incentives helped improved compliance and retention rate. The lessons learned to maintain a high retention and compliance rate in this study provide valuable insights for future studies in a similar population.

1. Introduction

Bone mass acquired during childhood is a key determinant for life-long skeletal health [1,2] and maximizing peak bone mass (PBM) can

help prevent osteoporosis. The gap between calcium intake and requirement to achieve PBM can be filled with inclusion of non-digestible carbohydrate compounds to improve calcium absorption largely through colonic fermentation [3–5]. In recent years, soluble corn fiber

Abbreviations: PBM, peak bone mass; BMD, bone mineral density; BMC, bone mineral content; SCF, soluble corn fibre; P1NP, procollagen type 1 amino-terminal propeptide; BAP, bone-specific alkaline phosphatase; CTX, carboxy-terminal collagen crosslinks; OC, osteocalcin; 25-OHD, serum 25-hydroxyvitamin D; iPTH, intact parathyroid hormone; DXA, dual-energy X-ray absorptiometry; MET, total metabolic equivalent.

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(SCF) has emerged as a prebiotic which enhances calcium absorption in animal and human trials [5,6]. However, long-term studies of SCF supplementation are needed to determine whether the enhanced calcium absorption can improve bone indices, in early pubertal children where the bone mass accrual and calcium retention is highest [7]. Therefore, we undertook a 1-year randomized double-blind placebo-controlled study to test the effects of supplementing SCF on bone indices of children aged 9–11 years.

It is well recognized by researchers that the efficacy and effectiveness of an intervention depends on successful recruitment and retention of participants. Slow recruitment would delay trial completion and increase study costs while loss of participants during trial follow-ups can reduce power affecting the generalizability, validity and reliability of results [8]. In general, participants losses of above 20% can threaten trial validity and approximately 45% of trials fail to recruit the necessary number of participants in the time planned [9,10]. Multiple approaches such as providing incentives, tracking methods, study benefits and community involvement have been reported to contribute to successful recruitment and retention in studies involving adult populations [11].

Studies reporting recruitment and retention rates among children are scarce. Children are considered vulnerable participants with different levels of cognitive development and abilities to provide informed consent [12]. Hence, recruitment and retention strategies need to consider ethical and legal implications including the extent of parental involvement to secure a representative sample and retention rates to ensure validity of study results. Previous studies in children have reported challenges due to parental mistrust of the research process, privacy concerns, and family time constraints [13–15].

In our study which is a nutrition intervention for 1-year, we anticipate factors such as demands of school schedules and exams, teachers and parents support, peer influence, taste fatigue and the ability to sustain a new behavior for long term as the biggest barriers to enroll participants and ensure compliance. This paper therefore aims to describe the study protocol, strategies used and the lessons learned to improve retention and intervention compliance in this longitudinal 1-year supplementation study of SCF in pre-adolescent children.

2. Methodology

2.1. Study design

PREBONE-Kids was a double-blind, randomized, parallel trial of 4 arms to investigate the effects of SCF supplementation on bone indices in children aged 9 to 11. Participants were randomized into 4 groups i.e. 600 mg calcium only (Ca), 12 g SCF only (SCF), 12 g SCF plus 600 mg calcium (SCF + Ca) and placebo. The participants consumed the intervention products for 1-year and measurements of outcomes were made at baseline, 6 months and 1-year.

Ethical approval was obtained from the Research and Ethics Committee of the International Medical University (IMU R/2016) and the trial was registered in clinicaltrials.gov (NCT03864172). The study was approved to be conducted in schools by the Ministry of Education, Malaysia (KPMSP.600-3/2/3). Informed consent was obtained from parents or legal guardians and assents obtained from the participants.

2.2. Study population

The study population were healthy, pre-adolescent boys and girls between 9 and 11 years old, living in Kuala Lumpur, Malaysia. Three schools within the vicinity of 10 km to the clinic that would perform the bone mineral density (BMD) measurements in the study agreed to participate and they were in the areas of Bangsar and Brickfields, Kuala Lumpur.

2.2.1. Eligibility criteria

The inclusion criteria were healthy as determined by a standard medical assessment, Tanner Stage 1 or 2 based on breast development for girls and pubic hair in boys, premenarcheal girls, willing to comply with study procedures and able to provide assent. Participants were excluded if they had a history of serious medical conditions and received therapy with medications known to interfere with bone metabolism (e.g. steroids, hormones, diuretics, cortisone or anti-seizure medication).

2.3. Intervention

Participants were provided with fruit-flavored powder (orange or blackcurrant) in sachets which they would mix in 200 ml of cold water to make a drink. Each sachet was approximately 80 kcal, 10 g carbohydrate with 8 g sugar and a negligible amount of protein and fat. Participants in the Ca group consumed 2 sachets each containing 300 mg calcium lactate gluconate while participants in the SCF + Ca consumed 2 sachets each containing 300 mg calcium lactate gluconate with 12 g SCF. Participant in the SCF alone group consumed 2 sachets each containing 12 g SCF. The placebo sachet did not contain any SCF or calcium but had the same appearance and taste as the treatment sachets. Calcium lactate gluconate was used in this study as due to its good solubility in cold water compared to other sources such as calcium carbonate [16]. All the participants were instructed to consume the intervention drink twice daily for 1-year.

2.4. Screening

Screening sessions were carried out at the schools for participants whose consents had been obtained from their parents to assess eligibility. The screening procedure included medical examination by a paediatrician, measurement of weight and height, determination of sexual maturation using the Tanner staging criteria and assessment of other eligibility criteria.

2.5. Study run-in

A study run-in was conducted before randomization into the actual study. Eligible participants were given the placebo powder to consume for 2 weeks during the study run in. They were given specific instructions to mix and consume the drinks twice a day and kept a diary of their daily intakes and recorded their food intakes for 3 days a week. At the end of the 2 weeks, participants who complied with the study protocol and able to consume the intervention drinks twice daily were enrolled into the study.

2.6. Randomization and blinding

Participants were randomized into 1 of the 4 treatment groups using a computer-generated software [17]. Randomization was block stratified by sex to ensure equal numbers of boys and girls in each treatment group. The participants, researchers and research assistants were blinded to the treatments throughout the study and analysis.

2.7. Study outcomes

BMD and bone mineral content (BMC) were the primary outcomes. The secondary outcomes were serum intact total procollagen type 1 amino-terminal propeptide (P1NP), bone-specific alkaline phosphatase (BAP), carboxy-terminal collagen crosslinks (CTX) and osteocalcin (OC). Other measurements include serum 25-hydroxyvitamin D (25-OHD) levels and intact parathyroid hormone (iPTH), and measurements of anthropometry, dietary intake and physical activity patterns.

2.8. Study measurements

All participants had baseline, 6th month and 12th month visits within specific time frame. Measurement's scheduling was either on weekends or after school hours to allow participants flexibility in choosing their appointments. The study time frame and measurements at each time point are presented in [Table 1](#).

2.8.1. Standard medical examination and pubertal stage

Participants were examined by a paediatrician on their health status using a standard medical examination at the schools. The pediatrician also interviewed the participants on their attainment of puberty and sexual maturation using the Tanner Stage pictorial guide [18,19].

2.8.2. Sociodemographic questionnaire

Demographic variables such as date of birth, ethnicity and household income were collected by interviewing the parents and participants at the schools.

2.8.3. Anthropometry, bone mineral density and body composition

Height and weight were measured using standard measurements and equipment. Body composition, BMD and BMC at the total body and lumbar spine (L1-L4) were measured using dual-energy X-ray absorptiometry (DXA) scan (GE Lunar iDXA, GE Healthcare, USA).

2.8.4. Biochemical parameters

A total of 6 ml of non-fasting blood were drawn to analyse for bone turnover markers (CTX, OC,P1NP and BAP which were analysed using electrochemiluminescence immunoassays while serum 25-

Table 1

Schedule of enrollment, interventions and measurements for study.

Activities	Enrollment	Timeline		
		Baseline	6 months	12 months
Informed consent	X			
Eligibility screening	X			
Study Run In	X			
Intervention				
Randomization	X			
Measurements				
<u>Medical examination</u>				
Standard medical examination	X	X		X
Tanner Staging	X	X	X	X
<u>Questionnaire</u>				
Socio demographic data		X		
Dietary intake		X	X	X
Physical activity		X	X	X
<u>Bone indices</u>				
Total body BMD/BMC		X	X	X
Lumbar spine BMD/BMC (L1-L4)		X	X	X
<u>Biochemical parameters</u>				
CTX		X	X	X
BAP		X	X	X
P1NP		X	X	X
OC		X	X	X
25-OHD		X		
iPTH		X		
<u>Anthropometry</u>				
Weight		X	X	X
Height		X	X	X
<u>Body composition</u>				
Fat free mass		X	X	X
Fat mass		X	X	X

Abbreviations: BMD: bone mineral density, BMC: bone mineral content; CTX; c-terminal telopeptide, BAP; bone alkaline phosphate, P1NP; procollagen type 1 N propeptide, OC; osteocalcin, iPTH; intact parathyroid hormone; 25-OHD:serum 25 hydroxyvitamin D.

hydroxyvitamin D (25-OHD) were determined by liquid chromatography tandem mass spectrometry (LC MS/MS).

2.8.5. Dietary intake

Dietary intakes at baseline were determined using a 7-day diet history while dietary intakes at 6 months and 12 months were determined using 3-day diet recalls. The dietary data were analysed using Nutritionist Pro diet analysis software (version 7.4.0, 2019, Axxya Systems, LLC, USA). Nutrients were analysed based on the database from Nutrition Composition of Malaysian Foods [20], Energy & Nutrient Composition of Singapore Foods [21] and nutrition labels on manufactured food products.

2.8.6. Physical activity

The physical activity level for the participants was measured using a validated physical activities questionnaire for children (cPAQ) Malay version adopted from Aini et al. [22]. Total metabolic equivalent task (MET) score (min/week) was calculated by multiplying the duration (minutes) and frequency (days) for each activity based on the scoring classification reported by Ainsworth et al. [23] and Kemper et al. [24].

2.8.7. Participants' feedback

At the end of the study, participants were asked on a voluntary basis to provide feedback on their satisfaction level of the overall study. The participants were provided with a set of questions to gauge their satisfaction level on the overall study conduct, activities conducted, taste of the intervention drinks, incentives provided and rapport with the research team.

3. Statistical analysis

3.1. Sample size calculation

The power analysis was calculated using the software OpenEpi [17] based upon BMD data from the study of inulin in children [3]. Sample size was calculated to be 240 based on 80% power using a two-sided 0.05 level *t*-test and assuming a 20% attrition rate. Each treatment arm consisted of 60 participants with an equal distribution of 30 boys and 30 girls.

3.2. Statistical analysis

Descriptive statistics (mean, standard deviation, frequency and percentage) were used to describe the baseline socio-economic characteristics, anthropometry, bone parameters, biochemical parameters, dietary intake and physical activity level of study participants. The baseline comparison between groups was tested using one-way ANOVA for continuous variables and Chi-square for categorical variables. Planned data analysis for the effects of the interventions would be compared using the Generalized Estimating Equation model (GEE) for intention to treat analysis, to evaluate the effect of group allocation, adjusting for time effect (time*group). Changes were controlled for growth (weight, height), sexual maturity (Tanner staging) and sex in the GEE models.

4. Strategies for recruitment, retention, compliance and lessons learned

4.1. Recruitment

A study brochure and a study information sheet along with informed consent and assent forms were distributed to a total of 1293 children from the Primary 3 to 5 grades through their class teachers in the 3 schools. Initial briefings were conducted to teachers during their weekly meetings to explain and clarify the purpose and procedures of the study. With permission from the school principals, the research

team set up study booths during various school activities such as sports day, canteen day and during the parent-teacher association (PTA) meetings. Briefings were also conducted about the study to the children during school assemblies. Study posters were placed at the schools and a WhatsApp chat group was set up at each school with the teachers to facilitate follow-ups with parents or students who have approached the teachers with interest to participate in the study.

4.1.1. Lessons learned

School-based recruitment was an effective strategy for the study. Approvals were needed in advance of recruiting in the schools from the Ministry of Education and at the district- and school-level. Gaining support from the teachers and parents of the potential participants were imperative for the successful recruitment of their student/child into the study. Teachers were concerned that the conduct of the study would interrupt lessons, and this was mitigated through recruiting from Primary 3 to 5 grades where students were not undergoing national examinations and limiting data collection only during recess or co-curriculum lesson times. Briefing the students directly during morning assemblies and meeting parents in schools were effective to explain the importance of bone health nutrition and the study objectives. Information provided on strategies to support compliance and proof on the Halal status of the interventional drink assured parents to allow their children to participate in the study. Another lesson learned was adopting a rolling recruitment strategy. As the study began with a small group of participants, the peer influence greatly assisted the recruitment process. Participants were more confident to join the study when they observed their friends' participation. The study run-in was a useful strategy to allow participants to experience the study protocol and to assess their readiness to make this commitment.

4.2. Compliance

Participants were fed one dose of the intervention drink at school from Mondays to Fridays during recess while the second dose was consumed at home. However, for participants whose compliance rate was less than 80%, both doses of the intervention drink were given at school by the study research assistants— during recess and after school hours. Parents were requested to monitor the participants' consumption during weekends and school holidays. Consumption fatigue or boredom set in within the first month of the study commencement. This was handled by allowing participants to switch flavours between orange and black-currant within the same treatment group.

Participants used a booklet to record their compliance using cartoon stickers to indicate number of sachets drank. Non-cash rewards (which were less than RM10 per gift) were given monthly in the form of stationaries, books and movie vouchers for those achieved 80% compliance and above. Fortnightly communication with parents through telephone calls or WhatsApp text messages were used to monitor compliance while troubleshooting related issues such as taste fatigue, missed drink and out-of-station travels. Compliance to the treatment intervention was calculated as a percentage of the actual number sachets of powder consumed each day compared to the expected consumption.

4.2.1. Lessons learned

The key strategy of ensuring compliance was the school feeding which was carried out during active school days, except on weekends and school holidays. This covered about 60% of the duration of the study. However, the lessons learned were adequate personnel/research assistants needed to be hired to travel to the schools on weekdays and the importance of the assistance from the teachers to ensure attendance of the participants to consume the drinks. School feeding provided an added advantage for participants with poor compliance because they were motivated when consuming the drinks together with their friends. Boredom or taste fatigue were a major hurdle to compliance and de-

spite permitting swapping of flavours, some participants were unable to comply with the rigid protocol of consuming the drinks every day. Incorporating fun into monitoring the intakes such as using cartoon stickers helped sustained the interests of the participants to perform this daily. Providing small rewards which were non-cash and allowing personal choice on the types of rewards each month was critical to maintain the motivation of the participants. Parents requested that rewards provided were useful for their child's learning or as school essentials.

4.3. Retention

All participants were given a T-shirt with a PREBONE-Kids emblem to create a sense of belonging to the study. Research assistants were assigned to support and monitor 8 to 10 participants and their parents via WhatsApp communication. Every month, nutrition information about bone health, growth and healthy recipes were shared with parents. Participants also received holiday greeting cards from the study team. Fun activities such as mini-carnivals, health talks by paediatricians and sports activities were conducted once every three months. During these activities in school, free health screening was also organized for parents and teachers. Parents received reports of their child's growth status alongside general dietary advice and have access to the paediatricians in the study for any consult of health concerns. Trips for bone density appointments were made on weekends and parents were reimbursed for their transportation costs to the centre.

4.3.1. Lessons learned

The main lesson learned relates to the importance of developing relationships with the participants and their parents. A significant amount of time was spent on building rapport and gaining trust from the participants. Meeting the participants daily in school and getting to know them on a personal level and being able to communicate using their native language and vocabulary were critical for rapport building. Keeping the parents engaged through social media platforms and providing access to health screening and general nutritional assessments for themselves and their child periodically in the school were a distinct advantage for sustaining the interest to stay in the study. Flexibility with dates and timing and the travel costs reimbursements for bone measurement appointments were important to minimise inconvenience and interruptions of daily schedules for the parents. The research assistant was the main contact person and was available for parents to address any difficulties or issues which may arise about their child's participation during the study. The constant effort to ensure a pleasant experience for the participants and their parents in every aspect of the study helped earned the trust of the participants to remain in the study.

5. Results

5.1. Recruitment and retention

Of the 1293 children invited to participate in this study, 293 positive responses (22.6%) were received and these children were invited to attend screening sessions conducted in their respective schools. A total of 278 participants attended the screening and 261 met the inclusion criteria and began the 2 weeks' study run-in. As a result of the study run-in, 18 (6.9%) of the 261 participants refused participation citing difficulty to comply to the study protocol ($n = 16$). Two participants transferred to non-study schools. This resulted in a successful recruitment meeting the target sample size of a total of 243 participants. They were then randomized into 1 of the 4 groups in the study with 60 participants in Ca group, and 61 participants in each of the SCF, SCF + Ca and placebo groups.

The overall retention rates of the participants at the end of 6 months and 1-year are shown in [Table 2](#). After 1-year, 201 participants completed the study yielding a drop-out rate of only 17.3%. Majority of the

Table 2
Study retention rates at baseline, 6 months and 12 months.

Time point	Retention (n,%)		
	Baseline (N = 243)	6 months (N = 204)	12 months (N = 201)
Intervention & Control			
600 mg Ca	60 (100.0%)	53 (88.3%)	52 (86.7%)
12 g SCF	61 (100.0%)	52 (85.2%)	51 (83.6%)
600 mg Ca + 12 g SCF	61 (100.0%)	47 (77.0%)	47 (77.0%)
Placebo	61 (100.0%)	52 (85.2%)	51 (83.6%)

participants dropped out at 6 months after the study commencement. The major reasons for not staying on the study were loss of interest to continue with the supplementation (n = 28), loss of contact (n = 3), transfer from study site (n = 3) and illnesses unrelated to intervention product such as hospitalisation, diagnosis of asthma and allergies (n = 8).

5.2. Compliance

The mean compliance rate at the beginning of the study was 85.0% (Table 3). As the study progressed, the compliance rate remained high at 78.7% at the end of the study. The compliance rate was similar across the 4 groups throughout the study. Low compliance (defined as < 50%) throughout the study was present in less than one fifth of the participants. Reasons for poor compliance among this group of participants were forgetfulness (70%) and boredom (30%) with the intervention drinks.

5.3. Baseline characteristics

Table 4 shows the baseline characteristics of the 243 participants who were enrolled and randomized into the study. Participants had a mean age of 10.1 ± 1.0 years and majority from Malay (90.5%) ethnicity. All participants were in early pubertal status with 230 of them in Tanner Stage 1 (boys: 125; girls: 105) while 13 of them were in Tanner stage 2 (boys: 2; girls: 11). The girls were premenarcheal at baseline. The participants mean weight was 34.0 ± 12.1 kg and 8.6% of them were thin while 17.7% were obese based on the WHO criteria [25]. The habitual calcium intake was 349 ± 180 mg/day (range: 218–459 mg/day) and 99.6% of the study participants did not meet their calcium recommended nutrient intake (RNI) [26]. The serum 25-OHD levels of the participants were low at 43.9 ± 14.5 nmol/L and only 57.6% of the participants were classified as having sufficient serum vitamin D according to the IOM vitamin D cut off values [27].

5.4. Participants' feedback

Table 5 shows the study satisfaction from a sub-set of 85 participants (42% of study completers) who voluntarily responded to provide feedback on the study conduct. Majority (above 95%) of the

Table 3
Compliance rates at initial, 6 and 12 months.

Trial period	Total	Ca (N = 52)	SCF (N = 51)	SCF + Ca (N = 47)	Placebo (N = 51)	p value
Initial 1st month	85.0 ± 30.0	83.8 ± 22.2	88.3 ± 25.2	84.7 ± 37.0	83.3 ± 33.5	0.794
6 months	82.9 ± 24.0	79.2 ± 23.6	85.7 ± 25.6	86.0 ± 20.6	81.0 ± 25.7	0.384
12 months	78.7 ± 23.8	74.4 ± 25.9	83.6 ± 22.8	80.3 ± 21.0	76.5 ± 24.6	0.209
Frequency of participants in categories of compliance (n,%)						
Good ≥80%	109 (54.2)	23 (43.4)	28 (56.0)	33 (64.7)	25 (53.2)	
Moderate 50–79%	58 (28.9)	18 (34.0)	11 (22.0)	13 (25.5)	16 (34.0)	
Poor <50%	34 (16.9)	12 (22.6)	11 (22.0)	5 (9.8)	6 (12.8)	

Mean compliance rate of participants expressed as mean ± SD. Comparison among groups tested with two-way ANOVA (p > 0.05).

participants informed that they were satisfied with the overall study conduct and activities. The participants were also satisfied with the incentives and rapport with the research team. The verbal feedback from parents included:

“ I liked it that the doctors and dietitians monitored my child's growth and health during the duration of the study. I find the information provided by them is useful indeed”

“ My son was happy to participate in this study as he liked interacting with the researchers as they spoke his language and connected with him through various activities”

“ I appreciate the constant interaction with the researcher as they keep me posted on my child's health and provided me healthful nutrition tips via WhatsApp”

6. Discussion

The PREBONE-Kids study will contribute to evidence on the long term effect of SCF and calcium, alone and together, on bone indices in early pubertal Asian children with habitual low calcium intakes. This double-blind placebo-controlled study is also the first calcium supplementation study among early pubertal children in Malaysia and will provide much needed data to understand the relationships of bone indices and nutrition status of early pubertal children in an Asian population.

Hence, it was imperative that efforts were made to improve retention and generate maximum data return in the study. The strategies implemented to recruit and retain participants were successful as the study achieved the targeted sample size of 243 participants and retained 82.7% of the participants at the end of 1-year. While there are no universally accepted criteria for retention rates in RCTs, it is generally recommended to not exceed 20% to avoid significant threats on validity and generalizability of the results [8].

One of the main considerations at the beginning of the study was to determine how best to recruit pre-adolescents for a long-term study. Recruiting from schools facilitated the process of tracing and contacting the participants because the majority remained in the same school throughout the 1-year period - only 3% of participants transferred schools in this study. The Ministry of Education imposed strict rules in the conduct of research to safeguard the best interest of school children and approval was not easily obtained from the authorities. Studies have shown that understanding cultural aspects and knowing what is important to study participants is a salient strategy for recruitment and retention [28,29]. This is further supported by our study as we had extensive discussions with the school authorities at the beginning of the study to understand our study population better. The discussions helped us to plan the study activities which focused on issues important to the study population and in line with their social cultural aspects. We met the parents physically or through the telephone to conduct active consent process even though the parents had given their signed consent through the forms distributed by the schools. Winter et al. (2018) states that accommodating to cultural aspects is important in conduct of clinical tri-

Table 4
Baseline characteristics of participants (N = 243).

Characteristics	Study participants (N = 243)
Age	10.1 ± 1.0
Gender (n,%)	
Boys	127 (52.3)
Girls	116 (47.7)
Ethnicity (n,%)	
Malay	220 (90.5)
Indian	23 (9.5)
Pubertal stage (n, %)	
Tanner 1	230 (94.7)
Tanner 2	13 (5.3)
Weight (kg)	34.0 ± 12.1
Height (cm)	135.8 ± 9.1
BMI (kg/m ²)	18.0 ± 4.5
BMI category (n, %)	
Thinness	21 (8.6)
Normal	142 (58.4)
Overweight	39 (16.1)
Obese	42 (17.3)
Lean mass (kg)	10.9 ± 7.1
Fat mass (kg)	21.8 ± 5.3
Pubertal stage (n, %)	
Tanner 1	230 (94.7)
Tanner 2	13 (5.3)
Energy intake (kcal/day)	1457 ± 450
Calcium intake (mg)	349 ± 180
Physical activity (MET)	822.5 ± 447.2
TB BMD (g/cm ²)	0.768 ± 0.075
TB BMC (g)	1129.45 ± 231.59
TB BMD Z-score	0.8 ± 1.0
LS BMD (g/cm ²)	0.725 ± 0.091
LS BMC (g)	21.73 ± 5.17
CTX (ng/ml)	0.96 ± 0.4
BAP (ug/l)	72.8 ± 25.3
P1NP (ng/mL)	617.1 ± 237.0
OC (ng/mL)	49.8 ± 21.7
Serum 25-OHD (ng/mL)	43.9 ± 14.5
Deficiency (<30 nmol/L)	46 (18.9)
Insufficient (30–40 nmol/L)	57 (23.5)
Sufficient (>40 nmol/L)	140 (57.6)
iPTH (pmol/L)	3.33 ± 2.14

Abbreviation: TB: total body; LS: lumbar spine; BMD: bone mineral density, BMC: bone mineral content; CTX: c-terminal telopeptide; BAP: bone alkaline phosphate, P1NP: procollagen type 1 N propeptide; P1NP; OC: osteocalcin, iPTH: parathyroid.

Data expressed as n (%) for ethnicity, BMI and pubertal staging while all other data is presented as mean ± SD.

Classification for serum 25-OHD is based on IOM 2011 [27].

Table 5
Feedback on the study conduct by voluntary response from participants (N = 85).

Domains	Satisfied n (%)	Not satisfied n (%)
Overall study conduct	81 (95.3%)	4 (4.7%)
Activities conducted	81 (95.3%)	4 (4.7%)
Taste of the supplement	77 (90.6%)	8 (9.4%)
Incentives provided	84 (98.8%)	1 (1.2%)
Rapport with research team	81 (95.3%)	4 (4.7%)

als in special population such as children [30]. Similarly in this study, we ensured that socio-economic and cultural aspects is considered in communication with participants and their parents by communicating in participant's language, providing halal certification of the supplementation and addressing issues with relevant holidays and religious activities. Additionally, the strategies of providing clear messages, creating study identity, utilizing dedicated phone lines and daily contact with participants in this study positively influenced the recruitment and retention rate similar to other findings [31,32]. The nature and per-

ceived benefits of the study played an important role to ensure retention and, in this study, the clinical benefit of closely monitored child's growth and dietary intake was perceived important by the parents. It was crucial to focus on the parents' priorities as parents were the ultimate decision makers in recruitment and retention of their children in the study [29,33].

The age of the participants did not pose a challenge as they were old enough to understand the study protocol and provide assent. Nevertheless, the degree of inconvenience involved in the study and the formation of a new daily habit of consuming the intervention drink for 1-year was a struggle that could hinder retention and compliance rate. Even though there are little published evidence on benefit of study run-in in pediatric clinical research, providing a study run-in with placebo drinks assisted this study participants and their parents to experience the study protocol and verbalize any of their concern prior to joining the study. It was interesting to note that most drop-outs occurred within the first 6 months of the study and the main reason for dropping out was related to compliance. Nevertheless, the study achieved a good compliance rate of 78.7% throughout the 1-year. This was mainly contributed by direct on-site school feeding of the drinks.

Offering rewards to the participants who made an effort to maintain compliance proved useful. Evidence on the use of incentives for clinical studies have the potential to improve both recruitment and retention [9], but should not be a form of coercion or undue influence to remain in the study especially in pediatric population [34]. The sub-set sample of participants who were willing to provide feedback on the manner of which the study was conducted expressed satisfaction on their experiences although it was a study limitation that they were not representative of the entire study population. Additionally, the positive relationship built between the researchers and the participants helped further enhance the compliance and retention rates of participants in this study.

7. Conclusion

The aim of PREBONE-Kids study is to provide evidence on the long term effect of SCF and calcium on bone indices in early pubertal Asian children with habitual low calcium intakes. Successful strategies focused on building rapport with the study participants and their parents through frequent WhatsApp messaging, fun school-based activities, direct on-site school feeding and non-cash incentives helped improved compliance and retention rate. The lessons learned from the strategies employed to achieve a high recruitment and retention rates is valuable for the conduct of future studies in a similar population.

Author's contribution

Arasu K: Investigation, Formal analysis, Data curation, Writing-original draft, Project administration **Chang CY:** Investigation, Data curation, Writing – review & editing **Wong SY:** Investigation, Data curation, Writing – review & editing **Ong SH:** Investigation, Writing – review & editing **Yang WY:** Investigation, Writing – review & editing **Chong MZH:** Investigation, Writing – review & editing **Meenal M:** Investigation, Writing – review & editing **Khoo EJ:** Investigation, Writing – review & editing **Karuthan C:** Formal analysis **Weaver CM:** Conceptualization, Writing – review & editing **Chee WSS:** Conceptualization, Methodology, Investigation, Writing – original draft, Visualization, Supervision, Project administration, Funding acquisition.

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Declaration of competing interest

The authors declare there are no conflicts of interest.

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References

- [1] A.D. Baxter-Jones, R.A. Faulkner, M.R. Forwood, R.L. Mirwald, D.A. Bailey, Bone mineral accrual from 8 to 30 years of age: an estimation of peak bone mass, *J. Bone Miner. Res.* 26 (8) (2011) 1729–1739.
- [2] D. Bailey, The saskatchewan pediatric bone mineral accrual study: bone mineral acquisition during the growing years, *Int. J. Sports Med.* 18 (S 3) (1997) S191–S194.
- [3] S.A. Abrams, I.J. Griffin, K.M. Hawthorne, L. Liang, S.K. Gunn, G. Darlington, et al., A combination of prebiotic short-and long-chain inulin-type fructans enhances calcium absorption and bone mineralization in young adolescents–, *Am. J. Clin. Nutr.* 82 (2) (2005) 471–476.
- [4] C.M. Whisner, B.R. Martin, M.H. Schoterman, C.H. Nakatsu, L.D. McCabe, G.P. McCabe, et al., Galacto-oligosaccharides increase calcium absorption and gut bifidobacteria in young girls: a double-blind cross-over trial, *Br. J. Nutr.* 110 (7) (2013) 1292–1303.
- [5] C.M. Whisner, B.R. Martin, C.H. Nakatsu, J.A. Story, C.J. MacDonald-Clarke, L.D. McCabe, et al., Soluble corn fiber increases calcium absorption associated with shifts in the gut microbiome: a randomized dose-response trial in free-living pubertal females, *J. Nutr.* 146 (7) (2016) 1298–1306.
- [6] C.M. Weaver, B.R. Martin, J.A. Story, I. Hutchinson, L. Sanders, Novel fibers increase bone calcium content and strength beyond efficiency of large intestine fermentation, *J. Agric. Food Chem.* 58 (16) (2010) 8952–8957.
- [7] S.A. Abrams, J.E. Stuff, Calcium metabolism in girls: current dietary intakes lead to low rates of calcium absorption and retention during puberty, *Am. J. Clin. Nutr.* 60 (5) (1994) 739–743.
- [8] M.S. Fewtrell, K.-S. Kennedy, S.A. Atul, R.M. Martin, A. Ness, M. Hadders-Algra, et al., How much loss to follow-up is acceptable in long-term randomised trials and prospective studies?, *Arch. Dis. Child.* 93 (6) (2008 Jun) 458–461.
- [9] B. Parkinson, R. Meacock, M. Sutton, E. Fichera, N. Mills, G.W. Shorter, et al., Designing and using incentives to support recruitment and retention in clinical trials: a scoping review and a checklist for design, *Trials* 20 (1) (2019) 624.
- [10] K.F. Schulz, D.A. Grimes, Sample size slippages in randomised trials: exclusions and the lost and wayward, *Lancet* 359 (9308) (2002) 781–785.
- [11] K.A. Robinson, V.D. Dinglas, V. Sukrithan, R. Yalamanhilli, P.A. Mendez-Tellez, C. Dennison-Himmelfarb, et al., Updated systematic review identifies substantial number of retention strategies: using more strategies retains more study participants, *J. Clin. Epidemiol.* 68 (12) (2015) 1481–1487.
- [12] D.E. Parrish, J.F. Duron, H.K. Oxhandler, Adolescent recruitment strategies: lessons learned from a university-based study of social anxiety, *Soc. Work. Res.* 41 (4) (2017) 213–220.
- [13] C. Baquet, Clinical trials: the art of enrollment, *Seminars in Oncology Nursing*, Elsevier, 2008.
- [14] P.H. Caldwell, S.B. Murphy, P.N. Butow, J.C. Craig, Clinical trials in children, *Lancet* 364 (9436) (2004) 803–811.
- [15] A.M. Gallo, E.K. Hadley, D.B. Angst, K.A. Knaf, C.A. Smith, Parents' concerns about issues related to their children's genetic conditions, *J. Spec. Pediatr. Nurs. (JSPN)* 13 (1) (2008) 4–14.
- [16] International Labor Organization (ILO), International chemical safety cards (ICSC). ILO international chemical safety cards (ICSC) . 13 April/2021; Available at: 19 April/2021 <http://www.ilo.org/dyn/icsc/showcard.home>.
- [17] M. Saghaei, Random allocation software for parallel group randomized trials, *BMC Med. Res. Methodol.* 4 (1) (2004) 26.
- [18] W.A. Marshall, J.M. Tanner, Variations in pattern of pubertal changes in girls, *Arch. Dis. Child.* 44 (235) (1969 Jun) 291–303.
- [19] W.A. Marshall, J.M. Tanner, Variations in the pattern of pubertal changes in boys, *Arch. Dis. Child.* 45 (239) (1970 Feb) 13–23.
- [20] E. Tee, M. Ismail, M. Nasir, K. Idris, Nutrient Composition of Malaysian Foods, fourth ed., Institute for Medical Research, Kuala Lumpur, 1987.
- [21] Health Promotion Board. Energy & Nutrient Composition of Food. (Available).
- [22] J. Nor Aini, B.K. Poh, W.S.S. Chee, Validity of a children's physical activity questionnaire (cPAQ) for the study of bone health, *Pediatr. Int.* 55 (2) (2013) 223–228.
- [23] B.E. Ainsworth, W.L. Haskell, M.C. Whitt, M.L. Irwin, A.M. Swartz, S.J. Strath, et al., Compendium of physical activities: an update of activity codes and MET intensities, *Med. Sci. Sports Exerc.* 32 (9; SUPP/1) (2000) S498–S504.
- [24] H. Kemper, I. Bakker, J. Twisk, W. Van Mechelen, Validation of a physical activity questionnaire to measure the effect of mechanical strain on bone mass, *Bone* 30 (5) (2002) 799–804.
- [25] M. Onis, A.W. Onyango, E. Borghi, A. Siyam, C. Nishida, J. Siekmann, Development of a WHO growth reference for school-aged children and adolescents, *Bull. World Health Organ.* 85 (2007) 660–667.
- [26] National Coordinating Committee on Food and Nutrition, Ministry of Health Malaysia, Recommended Nutrient Intakes for Malaysia. A Report of the Technical Working Group on Nutritional Guidelines, 2017.
- [27] Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Dietary Reference Intakes for Calcium and Vitamin D, The National Academies Press, 2011.
- [28] A.M. Nápoles, L.A. Chadiha, Advancing the science of recruitment and retention of ethnically diverse populations, *Gerontol.* 51 (suppl_1) (2011) S142–S146.
- [29] K. Woolfall, V. Shilling, H. Hickey, R.L. Smyth, E. Sowden, P.R. Williamson, et al., Parents' agendas in paediatric clinical trial recruitment are different from researchers' and often remain unvoiced: a qualitative study, *PloS One* 8 (7) (2013) e67352.
- [30] S.S. Winter, J.M. Page-Reeves, K.A. Page, E. Haozous, A. Solares, C.N. Cordova, et al., Inclusion of special populations in clinical research: important considerations and guidelines, *J. Clin. Transl. Res.* 4 (1) (2018) 56.
- [31] S. Schoeppe, M. Oliver, H.M. Badland, M. Burke, M.J. Duncan, Recruitment and retention of children in behavioral health risk factor studies: REACH strategies, *Int. J. Behav. Med.* 21 (5) (2014) 794–803.
- [32] L.M. Nicholson, P.M. Schwirian, E.G. Klein, T. Skybo, L. Murray-Johnson, I. Eneli, et al., Recruitment and retention strategies in longitudinal clinical studies with low-income populations, *Contemp. Clin. Trials* 32 (3) (2011) 353–362.
- [33] R.G. Greenberg, B. Gamel, D. Bloom, J. Bradley, H.S. Jafri, D. Hinton, et al., Parents' perceived obstacles to pediatric clinical trial participation: findings from the clinical trials transformation initiative, *Contemp. Clin. Trials Commun.* 9 (2018) 33–39.
- [34] R.E. Behrman, M.J. Field, Ethical Conduct of Clinical Research Involving Children, National Academies Press, 2004.