



DATA NOTE

Using SITAR (SuperImposition by Translation and Rotation) to estimate age at peak height velocity in Avon Longitudinal Study of Parents and Children [version 1; referees: 2 approved]

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Abstract

Puberty is a time of substantial biological and psychological changes. One of the hallmarks of puberty is a rapid growth spurt, however its timing varies between individuals. The impact of pubertal timing on later health outcomes has been of interest in life course epidemiology, however its measurement can be challenging. Age at peak height velocity (aPHV) offers an objective measure of pubertal timing without having to rely on physical examination or self-report. We describe the derivation of aPHV estimates in Avon Longitudinal Study of Parents and Children (ALSPAC) offspring, using Superimposition by Translation And Rotation (SITAR) mixed effects growth curve analysis. ALSPAC is a rich source of phenotypic and genotypic data and given the importance of pubertal timing for later health outcomes, these data offer an opportunity to explore the determinants and consequences of aPHV.

Keywords

ALSPAC, pubertal timing, growth, age at peak height velocity



This article is included in the [Avon Longitudinal Study of Parents and Children \(ALSPAC\) gateway](#).

Open Peer Review

Referee Status:

	Invited Referees	
	1	2
version 1 published 25 Jul 2018	 report	 report

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John M. Pettifor , University of the Witwatersrand, South Africa
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Competing interests: No competing interests were disclosed.

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Introduction

Puberty is a period of significant biological and psychological changes in human development. One of its hallmarks includes a rapid growth spurt, the timing and speed of which varies between individuals, with marked sexual dimorphism.

The relationship of pubertal timing with adverse health outcomes in later life has been investigated previously¹. For example, previous studies reported an association between late menarche and increased risk of osteoporosis², whereas early pubertal timing has been found to be related to higher risk of obesity and cardiovascular disease in both men and women³. Thus, investigating the influences of pubertal timing and understanding its relationship with later health outcomes is of great public health importance. While clinical assessment remains the gold standard for the assessment of pubertal status, this is difficult to achieve in large-scale studies. Self-reported puberty measures lack reliability^{4,5}, and may be unpopular with study participants, potentially leading to large amounts of missing data. Another measure, age at peak height velocity (aPHV) provides an objective and non-invasive assessment of pubertal status.

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a longitudinal birth cohort, which was established in the 1990s in the South West of England⁶. ALSPAC is a rich source of data, including phenotypic and genetic data collected for the mothers, fathers and children.

This paper describes the application of Superimposition by Translation And Rotation (SITAR) mixed effects growth curve model (described previously by Cole *et al.*⁷) for analysis of height in puberty and estimating aPHV in ALSPAC offspring which resulted in a new dataset being generated. Previous studies have shown this to be a suitable method for estimating aPHV⁸, even with fairly sparse data⁹.

Methods

ALSPAC recruited a total of 14,541 pregnant women with expected delivery date between 1st April 1991 and 31st December 1992. Of these pregnancies, 68 have no known birth outcome, 195 were twin, 3 were triplet and 1 was quadruplet. In total, these pregnancies resulted in 14,062 live births of which 13,988 children were alive at 1 year of age.

In order to increase sample size additional recruitment took place when the children were on average 7 years old (Phase II) and again between age 8 – 18 years (Phase II) resulting in a total of 15,247 enrolled pregnancies, of which 14,701 were alive at 1 year of age. For more details regarding eligibility and recruitment please refer to Boyd *et al.*⁶.

These children have been followed up from birth (those recruited during Phases II and III were followed up from the time they joined the study) and data collection included questionnaires and clinical assessments. For the purpose of estimating age at PHV, only height measurements obtained by trained fieldworkers during assessment clinics were used. These clinics encompassed ‘children in focus clinics’ (CIF) to which a

random 10% subsample of children were invited between the age 2 and 5 years, and six assessment clinics in late childhood (between age 7 and 13 years), three further assessment clinics in adolescence (ages 13, 15 and 17 years). These data were restricted to include height measurements collected when the children were between 5 to 20 years of age which resulted in a total of 61,290 height measurements available for 10,236 participants of whom 5,099 were female and 5,137 were male. To maximise accuracy of estimate aPHV, these data were further restricted to include individuals with at least one height measurement for the following time periods: 5 to <10 years, 10 to < 15 years and 15 to 20 years. A total of 46,246 height measurements for 5,707 individuals (3,019 females, 2,688 males) were available for SITAR analysis.

SITAR is a mixed effects shape-invariant growth curve model, consisting of a mean growth curve along with three transformations (size, tempo and velocity), used to describe how each individual differs from the mean curve. The three SITAR parameters are size, reflecting up/down shift from the mean curve; tempo, reflecting left/right shift (on the age scale) which corresponds to the relative timing of puberty based on aPHV, and velocity reflecting stretching/shrinking of the age scale and hence describing differences in the rate at which individuals pass through puberty. For a detailed description of the method please refer to Cole *et al.*⁷.

Height data were uploaded into R and following outlier removal of people with velocity exceeding 4 SDs (using `velout` function; for more details see `sitar` package documentation in R¹⁰), an initial SITAR model was fitted, for males and females separately, in R version 3.4.1. Following initial model fitting, standardized residuals exceeding 4 in absolute value were removed leaving a total of 40,037 height measurements for 5,707 individuals available for analysis with an average of 8 measurements (range 1–10 measurements) available per participant (see [Figure 1](#) for details regarding participant recruitment).

Dataset validation

The final SITAR model was fitted with 5 degrees of freedom, for males and females separately, and it explained 98% and 98.3% of variance in the dataset for males and females, respectively. Mean aPHV (SD) was 13.6 (0.9) for males ([Figure 2](#)) and 11.7 (0.8) for females ([Figure 3](#)) and these estimates are similar to those reported in the literature^{11,12}.

[Table 1](#) shows mean and SD of additional variables that were estimated, which include: size (cm) (negative values indicating smaller whereas positive taller children and zero represents the mean), tempo (years) (negative values indicating early puberty, positive late puberty and zero represents the mean), velocity (years) (measure of intensity, positive values indicating short growth spurt, zero corresponding to mean velocity) along with peak velocity (cm).

Ethical approval and consent

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics

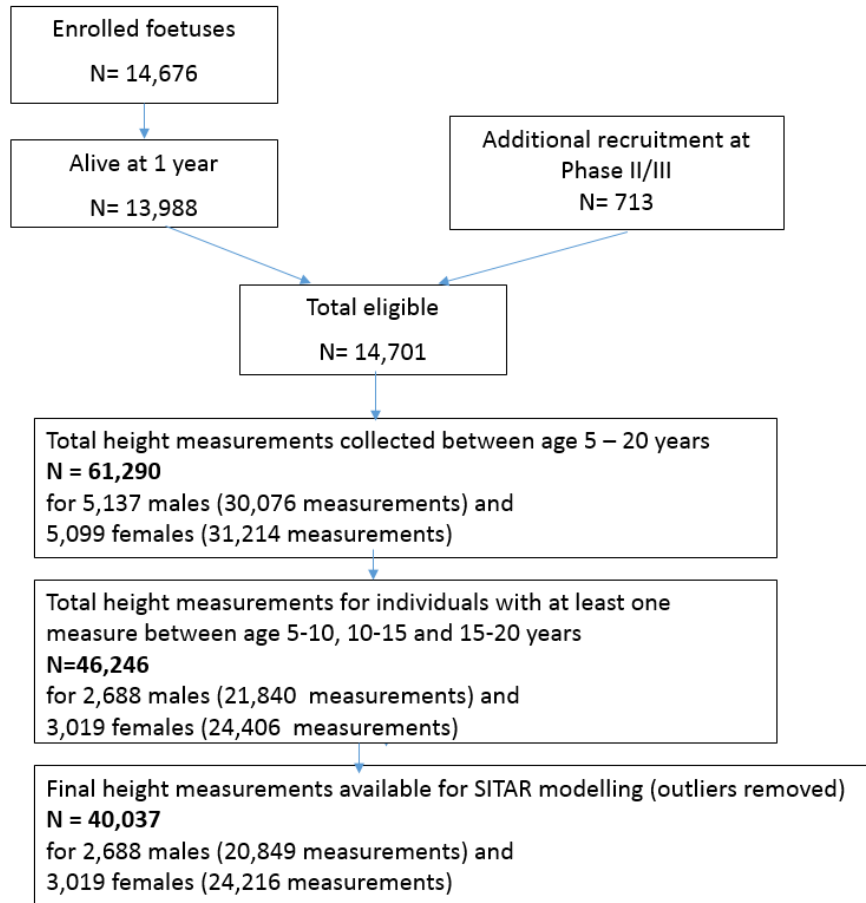


Figure 1. Avon Longitudinal Study of Parents and Children (ALSPAC) participant recruitment and height measurements available for analysis.

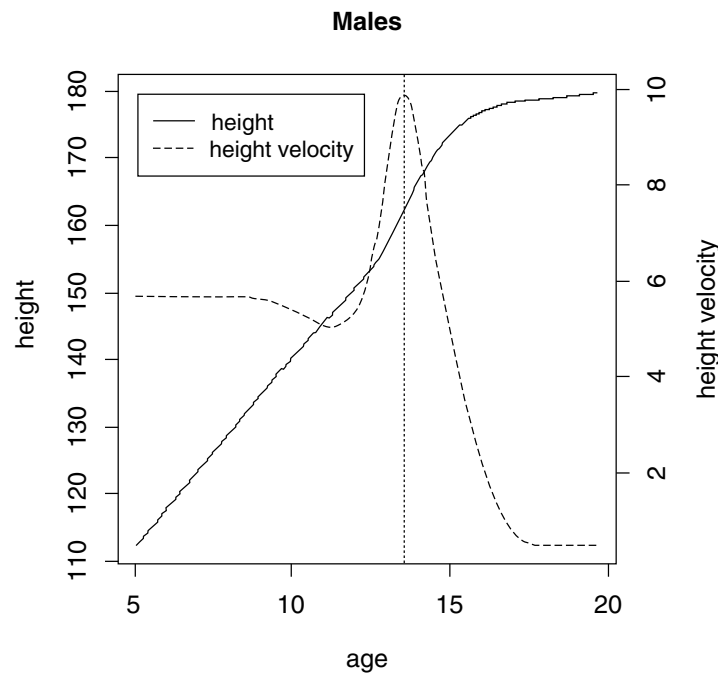


Figure 2. Mean growth curve (solid line) and velocity (dashed line) plots estimated by Superimposition by Translation and Rotation (SITAR) for males. Vertical dotted line represents mean age at peak height velocity.

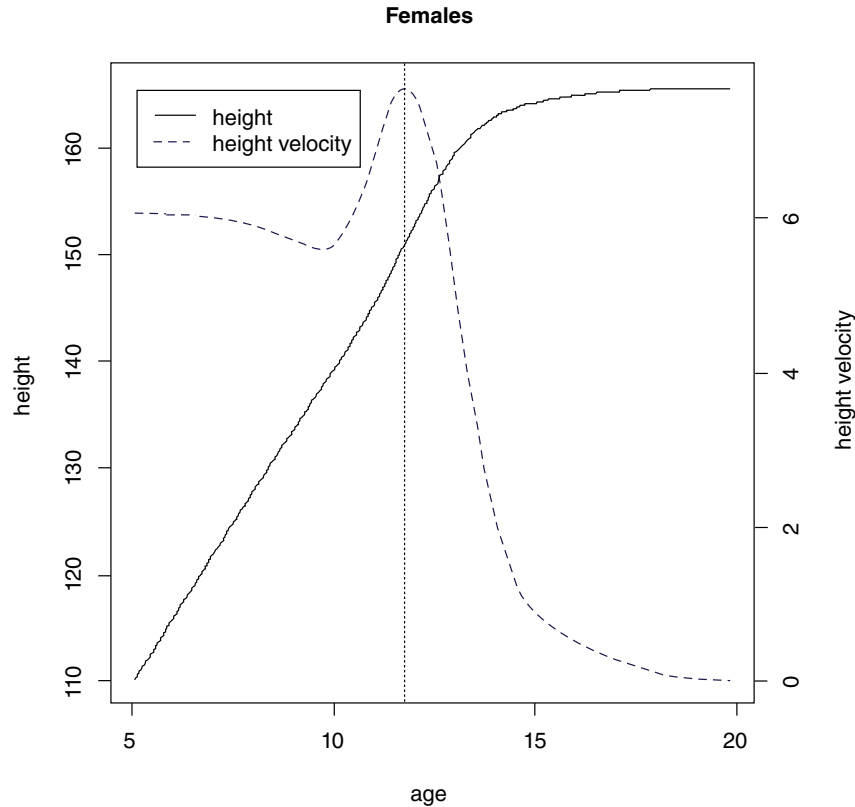


Figure 3. Mean growth curve (solid line) and velocity (dashed line) plots estimated by Superimposition by Translation and Rotation (SITAR) for females. Vertical dotted line represents mean age at peak height velocity.

Table 1. Means and standard deviations of estimated SITAR growth parameters in Avon Longitudinal Study of Parents and Children (ALSPAC) offspring.

	Combined (N= 5,707)	Males (N=2,688)	Females (N=3019)
Variable name	Mean (SD)	Mean (SD)	Mean (SD)
aPHV (years)	12.6 (1.3)	13.6 (0.9)	11.7 (0.8)
Size (cm)	0.0 (6.3)	0.0 (6.5)	0.0 (6.0)
Tempo (years)	0.0 (0.9)	0.0 (0.9)	0.0 (0.9)
Velocity (years)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)
Peak velocity (cm)	8.8 (1.5)	10.0 (1.1)	7.7 (0.8)

Abbreviations: aPHV (age at peak height velocity), SD (standard deviation)

Committees, full details of the approvals obtained are available from the study website (<http://www.bristol.ac.uk/alspac/researchers/research-ethics/>).

Written informed consent was obtained from parents, and children were invited to give consent where appropriate. Study members have the right to withdraw their consent for elements of the study or from the study entirely at any time.

Data availability

ALSPAC data access is through a system of managed open access. The steps below highlight how to apply for access to the data included in this data note and all other ALSPAC data. The

dataset generated in this data note has been deposited within the ALSPAC data resource and is linked to ALSPAC project number B2325. Please quote this number to request required variables which have been described in this dataset (size, tempo, velocity, aPHV and peak velocity).

1. Please read the [ALSPAC access policy \(PDF, 627kB\)](#) which describes the process of accessing the data and samples in detail, and outlines the costs associated with doing so.

2. You may also find it useful to browse our fully searchable [research proposals database](#), which lists all research projects that have been approved since April 2011.

3. Please [submit your research proposal](#) for consideration by the ALSPAC Executive Committee using the online process. You will receive a response within 10 working days to advise you whether your proposal has been approved.

If you have any questions about accessing data, please email alspac-data@bristol.ac.uk.

The ALSPAC data management plan describes in detail the policy regarding data sharing, which is through a system of managed open access.

Competing interests

No competing interests were disclosed.

Grant information

This work was supported by the Wellcome Trust through a PhD Studentship to MF [105504] and the ALSPAC core programme grant [102215].

The UK Medical Research Council and Wellcome [102215] and the University of Bristol provide core support for ALSPAC. LDH is supported by a Career Development Award fellowship from the UK Medical Research Council [MR/M020894/1]. MF, LDH and LP work in a unit that receives support from the UK Medical Research Council and the University of Bristol [MC_UU_12013/4 & MC_UU_12013/5].

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Frysz and colleagues provide a valuable Data Note, describing the calculation of age at peak height velocity and associated parameters using the SITAR technique (reference 7 in the paper) in the ALSPAC cohort. This technique reduces the complex information inherent in longitudinal measures of anthropometry to a smaller number of biologically-interpretable parameters. The authors have clearly reported the methods used and we anticipate that the availability of these new growth parameters, alongside the information provided in this Data Note, will add significant value to the ALSPAC dataset as an epidemiological resource for the study of timing of puberty.

We noted that the authors have removed outliers with velocity exceeding 4SDs which appears to be a reasonable method of dealing with clear measurement error. However, it leads to questions as to whether there were any individuals with velocity below -4SDs, or size or tempo parameters below -4SDs or above +4SDs. Why did the authors only remove those with velocity exceeding 4SDs?

The analyses in this paper were restricted to participants with at least one height measurement in the time periods 5 to <10 years, 10 to <15 years and 15 to <20 years. Could the authors describe why they chose these age brackets? Also, the Methods of the paper could clarify that the assessment clinics in late childhood and adolescence are were not restricted to the 10% 'children in focus' sample; currently the description is somewhat ambiguous.

Once the SITAR parameters of size, tempo and velocity have been calculated, two further variables have been created for each individual; 'peak height velocity' and 'age at peak height velocity'. It would be helpful if the authors could state specifically that these have been generated since age at peak height velocity is likely to be the output of greatest utility to future analysts using these data. There is also potential confusion within the manuscript that 'peak height velocity' and 'age at peak height velocity' both sound rather similar to the SITAR 'velocity' parameter – the authors might clarify that they are separate variables. In Table 1, the units for peak velocity should presumably be cm/year. Also, it would be useful if all three of the axes in Figures 2 and 3 had units added.

We noted two numerical discrepancies within the paper. Firstly the text describes 14,541 pregnant women recruited to the ALSPAC study, whereas 14,676 enrolled foetuses are shown in Figure 1; this difference doesn't appear to be attributable to multiple births. Secondly, the numbers of male and female measurements available for SITAR modelling in Figure 1 do not add to the total number of measurements (i.e. $20,849 + 24,216 \neq 40,037$).

The paper describes how 46,246 height measurements were available before considering potential measurement error. Outliers were removed with absolute velocity exceeding 4SDs and after initial model fitting those with absolute standardised residuals exceeding 4SDs were also removed. This left 40,037 height measurements available for SITAR modelling, a reduction of 13%. Since 0.006% of a normal distribution lies below -4SDs or above 4SDs, this is a surprising reduction in number of measurements, even in the context of a significant amount measurement error; a comment on this would be helpful.

The abstract ends with a helpful allusion to the opportunities afforded by these new measures available in the ALSPAC study. It would enhance the paper if the end of the Methods section could similarly describe how these measures might be used in the future. In particular the rich phenotype data available in ALSPAC provides the opportunity to consider an extensive range of both determinants and consequences of age at peak height velocity; the age at peak height velocity variable could further be utilised as a confounder or mediator in a wide range of analyses.

In addition we note the following minor points of wording:

The second line of the second column of page 3 would better read “between the ages of 2 and 5 years”.

Similarly, the ninth line of the second column of page 3 might be better worded “To maximise accuracy of the estimate of aPHV,”.

Is the rationale for creating the dataset(s) clearly described?

Yes

Are the protocols appropriate and is the work technically sound?

Yes

Are sufficient details of methods and materials provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Statistics, epidemiology

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 16 August 2018

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Frysz and colleagues from the University of Bristol describe the use of the statistical programme, Superimposition by Translation and Rotation (SITAR), to determine the age of peak height velocity (aPHV) in a cohort of children participating in the Avon Longitudinal Study of Parents and Children (ALSPAC). The results they obtained for both boys and girls (13.6 years and 11.7 years respectively) are similar to those obtained by other researchers in well-resourced countries.

SITAR, a recently developed modelling approach by Tim Cole¹, has been used increasingly in longitudinal studies to describe secular and population trends in childhood growth and pubertal development using skeletal development (Tanner RUS score) and aPHV in both poorly- and well-resourced communities²⁻⁴. Its advantages are that it assesses each individual's curve against the mean curve and is able to determine the size (amplitude of change), tempo (the timing of the onset of change) and velocity (rate of change) of each individual curve in relation to the mean curve. It is also robust with missing data. Cole in a paper published this year assessed the interval required between height measurements in individual adolescent children to optimize the determination of aPHV⁵. Cole concluded that height measurements need not be taken more frequently than biennially to obtain an accurate assessment of the average aPHV.

The reviewers have a few minor comments, which might help to provide further clarity on the participants included in the cohort. The authors describe the recruitment of participants from the ALSPAC cohort and the inclusion criteria for height measurements to be included into the database used for this particular aspect of the study. It is however unclear if black or Asian children were included in the analytical cohort sample. The reason for this comment is that data are available to suggest the age of pubertal development and aPHV in black children may differ from that of white children living in both well- and poorly-resourced countries^{3,6}. Thus their inclusion might have influenced the mean values of aPHV obtained and the subsequent comparisons with other cohorts.

The inclusion of an individual into the SITAR study required that at least one height measurement was available at each of three different time periods, 5-<10 years, 10-<15 years and 15-20 years. Yet in their analysis of the average number of measurements available per individual, the average is given as 8 with a range from 1-10. It is unclear how children with only one measurement were included based on the criteria for inclusion given above. It is possible that the authors meant that the participants included had at least one measurement in any of the age bands.

In the second paragraph of the Methods section, line 3, Phase II is referred to as being between age 8 - 18 years. We believe this should be Phase III.

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Is the rationale for creating the dataset(s) clearly described?

Yes

Are the protocols appropriate and is the work technically sound?

Yes

Are sufficient details of methods and materials provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
