RESEARCH ARTICLE

MOTIVES FOR GROWTH ENHANCING HORMONE TREATMENT IN YOUNG ADOLESCENTS WITH IDIOPATHIC SHORT STATURE OR INTRA-UTERINE GROWTH RETARDATION: A QUESTIONNAIRE AND STRUCTURED INTERVIEW STUDY

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ABSTRACT

Background
Growth enhancing hormone treatment is considered a possible intervention in short but otherwise healthy adolescents. Although gain in height is an obvious standard to evaluate hormone treatment, it is not the ultimate goal. It is a means to reach other goals such as avoidance of current height-related problems or the enhancement of future chances in life and society. The aim of our study was to clarify the possible motives for children and their parents to choose to participate in a growth enhancing trial combining growth hormone and puberty delaying hormone treatment.

Methods
Early pubertal adolescents (25 girls, 13 boys) between the ages of eleven and thirteen (mean age 11.5) years with idiopathic short stature or intrauterine growth retardation and their parents were examined by questionnaires and a structured interview regarding presence of height related stressors, parental worries about their child’s behavior and future chances, self-reported problems in psychosocial functioning, and treatment expectations. Questionnaire scores were compared to norms of the general Dutch population.

Results
The adolescents reported normal psychosocial adjustment and high expectations of treatment in terms of gain in height, whereas the parents reported that their children encountered some modest behavior problems (social, anxious/depressed, and attention problems) and height-related stressors (being teased and juvenilized). About 40% of the parents were worried about their children’s future chances to find a partner or job. Rather mixed profiles of motives for
the adolescents and their parents were found. Most clear were parental worries about current or future functioning of their children, while a smaller number of cases was characterized by no observed motives at all or psychosocial problems as reported by the adolescents themselves.

**Conclusions**

The motives of parents to let their children participate in a growth enhancing hormone trial are more clear than the motives of the adolescents. Individual differences in motives imply that in a proper evaluation of hormone treatment, different outcome variables are differently important for different individuals. Perhaps especially the observed psychosocial problems could also be approached with psychosocial counseling. Effectiveness evaluations of hormone treatment to solve the problems and to fulfill the divergent expectations must be awaited.
BACKGROUND

Short stature is a physical characteristic that has been associated with psychosocial disadvantages such as discrimination in the workplace and problems in psychosocial functioning including poor social competence, depressive feelings, and anxiety [1]. Although the short stature of the majority of people is without apparent pathology (idiopathic), a subgroup of children with idiopathic short stature visits a pediatrician because of their height. For these children growth enhancing hormone treatment is considered a possible intervention. In medical trials, gain in height is an obvious standard to evaluate hormone treatment. However, gain in height is not the ultimate goal. It is a means to reach other goals such as avoidance of current height-related problems or the enhancement of future chances in life and society.

Of all variables that are considered motives to want to gain height by hormone treatment, especially the psychosocial functioning of children with idiopathic short stature has been examined. Children who have never been medically referred do not seem to suffer from their stature [2-5]. Studies among medically referred children generally revealed reduced social competence [6-15], while internalizing and externalizing behavior, body image, self-esteem, and scholastic competence have been shown – on average – to be between normal and deviating in a negative way from normal [6-9, 11-18]. Besides the possibility to alleviate psychosocial suffering, several other factors are hypothesized to motivate children and their parents to choose hormone treatment: how medical referral has been brought about (e.g. by a family physician on parental initiative or by a school physician after routine check-up), the experience of height-related psychosocial stressors (such as being teased or juvenilized), future expectations to find a partner or a proper job, and expectations of treatment effects in
terms of gain in height. Moderator variables as gender and intelligence may influence these motives.

Insight into the divergent motives at the time of choosing hormone treatment is important, because it will help in the proper evaluation of a trial. Moreover, it will clarify whether other treatments, such as psychosocial counseling, can be considered to solve current psychosocial problems and reach future goals. Insight into motivational factors is especially important in treatments combining biosynthetic growth hormone with a puberty delaying hormone, because possible benefits of enhancing growth must be balanced against the possible negative psychosocial consequences of delaying pubertal development.

In the current study, we examined 38 early pubertal adolescents with idiopathic short stature (ISS) or intra-uterine growth retardation (IUGR). Adolescents with ISS have a height below two standard deviations from the mean for age and sex without an apparent underlying pathology [19], while adolescents with IUGR had a birth length of less than two standard deviations below the mean for gestational age [20]. The adolescents were medically referred to participate in an experimental trial of a combined treatment of growth hormone and a puberty delaying hormone versus no intervention. We examined the baseline scores of the adolescents before initiating the treatment with the aim to clarify the possible motives for parents and children to choose to participate in the trial.
METHODS

Study Population and Procedures

The study population consisted of 38 early pubertal adolescents (25 girls and 13 boys) between the ages of eleven and thirteen (mean age 11.5), with idiopathic short stature (17 girls, 9 boys) or intrauterine growth retardation (8 girls, 4 boys).

In the multi-center study, the University Medical Center Utrecht - Wilhelmina Children’s Hospital, the VU University Medical Center Amsterdam, the Sophia Children’s Hospital Rotterdam and the Catharina Hospital Eindhoven participated [21]. The adolescents, who were referred to the Departments of Pediatrics because of growth failure, were asked to participate in a controlled trial. After randomization, 50% of the adolescents were planned to receive combined treatment of growth hormone (GH) and the puberty delaying hormone Gonadotropin Releasing Hormone Agonist (GnRHa). The combined treatment was chosen, because it is supposed that GH has more effect on final height when the acceleration of pubertal development and bone maturation is delayed. During three years the adolescents in the treatment group would be given every four weeks intramuscularly in a depot preparation 3.75 mg GnRHa (Decapeptyl-CR, Ferring, Sweden) and daily by subcutaneous injection 4 IU (1.33 mg) per square meter body surface GH (Genotropin, Pharmacia, Sweden; at present Pfizer, New York, USA). The adolescents in the control group would be followed to document their growth and pubertal development [21].

Inclusion criteria for taking part in the study were: being in early puberty as documented by Tanner breast stage II or III in girls and Tanner genital stage II or III in boys, an actual height less than -2.0 standard deviation (SD) or between –1.0 and –2.0 SD with a predicted adult height less than -2.0 SD, a chronological age and bone age less than 12 years in girls and 13 years in boys, a documented growth hormone response of >20 mU/L (>10ug/L)
after a standard provocation test and/or during a sleep test, a ratio of sitting height/subischial leg height between P3 and P97, and normal blood tests and urinalysis.

A skilled psychologist examined the adolescents and their parents in the interval between randomization and start of the treatment. The adolescents filled out questionnaires on perceived competence, psychological distress, body image and self-image, and personality characteristics. The parents filled out questionnaires regarding emotional and behavioral problems of their children and were interviewed by a psychologist.

The medical ethics committees at the four participating centers approved the study. The parents of all children gave written informed consent before participating.

**Measures**

*Parental reports*

Parents were interviewed by means of a structured interview. They were asked about the health related development of their child: possible neonatal problems, health problems, and food intake of their child, the child’s age at which a physician was consulted for the first time because of the growth retardation, and who had been brought about the referral (school doctor, family doctor, or pediatrician). In order to find out which height-related psychosocial stressors the adolescents encountered, the parents answered (yes/no) whether their children were a) teased, b) neglected, c) juvenilized or d) being treated as normal by other children. To find out parents’ worries about their child’s future, the parents were asked whether they expected their child to have equal chance as persons of normal height on the labor market as an adult, and to find a partner (yes, doubtful, no).

To assess behavioral and emotional problems, the parents filled out the Child Behavior Check List (CBCL) [22]. This questionnaire consists of eight syndrome areas (the so-called
narrow-band scales): withdrawn behavior, somatic complaints, anxious/depressed behavior, social problems, thought problems, attention problems, delinquent behavior and aggressive behavior. The scores of the subscales were summarized in a score for internalizing (e.g., withdrawn and anxious/depressed) and externalizing (e.g., aggressive and delinquent) problems, and a total problem score (the so-called broad-band scales).

To measure perception of present and future height of the adolescents, the Silhouette Apperception Technique (SAT) was used. Drawings of different height were presented, corresponding proportionally with the heights of (in this sequence) percentiles 75, 25, 97, 50, 3, and 75. The parents were asked to identify the drawings which they thought to fit best the current and future height of their child.

**Self-reports**

Questionnaires regarding perceived competence, psychological distress, and personality characteristics were administered to the adolescents and the global level of cognitive functioning (intelligence) was examined.

The Dutch version of the Self Perception Profile for Children (CBSK) or Adolescents (CBSA) was used[23, 24]. The CBSK consists of six perceived competence subscales: scholastic ability, social acceptance, athletic ability, physical appearance, behavior and conscience, global self – worth. The CBSA consists of the same six scales plus the scales friendship and romantic love. In our study we only used the six scales that the CBSK and the CBSA have in common.

To measure anxiety, the Dutch version of the State-Trait Anxiety Inventory for Children (ZBV-K), with subscales state anxiety and trait anxiety, was used [25]. Depressive mood was assessed with the KDVK (short depression questionnaire for children) [26].
Personality characteristics of the adolescents were investigated by means of the Dutch Personality Questionnaire-junior (NPV-J), with five subscales: inadequacy, perseverance, social inadequacy, recalcitrance, dominance [27].

The Silhouette Apperception Technique (SAT) was used to measure perception of present and future height of the adolescents.

Intelligence was assessed by the Dutch short form of the Wechsler Intelligence Scale for Children (Revised) [28].

**Data Analyses**

Norm deviation scores were used to compare results of the quantitative questionnaires with means of the general Dutch population: mean scores of the appropriate age and sex norm group were subtracted from the individual raw scores (on the several subscales) of our study group. T-tests examined whether these age and sex adjusted scores significantly deviated from zero (the norm). To explore the role of potential risk- and protective factors, we used t-tests for independent samples and correlations (Pearson or Spearman where appropriate).

To classify subgroups of adolescents with divergent motives for wanting hormone treatment, we formed subgroups based on the presence of height related stressors (being teased or juvenilized), parental worries about future chances (regarding finding a partner or job), parental worries about their child’s behavior (internalizing problems or externalizing problems), and self-reported problems in psychosocial functioning (low self-esteem, anxiety, or depression). The cut-off score for having externalizing or internalizing problems was a norm deviation score of at least one standard deviation higher than the mean for age and sex on the CBCL-scales for internalizing and externalizing behavior problems. The cut-off score for low self-esteem and anxiety was a norm deviation score of at least one standard deviation
lower (self-esteem) or higher (anxiety) than the mean for age and sex on the global self-worth scale and the trait anxiety scale. The cut-off score for indicating clinical signs of depression was a raw score of 4 or more on the depression scale [26].
RESULTS

Medical referral

The mean age of the child when a physician was consulted for the first time because of the growth retardation, was 7.3 years (SD = 3.5). Medical referral had been brought about by the family physician (53%; 7 adolescents with IUGR, 13 with ISS) or school physician (23.5%; 2 adolescents with IUGR, 7 with ISS), whereas part of the adolescents was as a young child already under supervision of a pediatrician because of other health problems than short stature (23.5%; 3 adolescents with IUGR, 6 with ISS). Ninety percent of the parents reported that their children never had experienced serious health problems.

Height-related psychosocial stressors and future expectations

According to 62.9% of the parents their children were treated the same as adolescents with normal height, while 27.8 % reported that peers teased their children because of their short stature, and 13.9 % reported juvenilization. All but one adolescent took part in gymnastic lessons at school (97.3%).

With respect to future expectations, 41.7% of the parents expected their child to have less chances on the labor market when they would have grown up; 45.8% expected their child to have less chance to find a partner because of short stature.

Psychosocial functioning

Parental reports

On parental ratings of behavioral difficulties as measured by the CBCL, the short adolescents had higher scores than the norm group on the broad-band scales ‘internalizing behavior’ and ‘total behavior problems’ (Table 1). A trend towards significance was observed for
‘withdrawn behavior’, while the score on ‘anxious/depressed behavior’ was significantly higher. Both narrow-band scales load on the internalizing scale. The adolescents also obtained higher than normal scores on the scales ‘social problems’ and ‘attention problems’. In terms of effect sizes, the scores deviated 0.50 to 0.73 standard deviations from the norm (see Table 1). This reflects moderate deviations. Three adolescents obtained a clinical high score (deviation of more than two standard deviations) on internalizing behavior.

The short adolescents did not score significantly higher than the norm group on the narrow-band scales ‘somatic complaints’, ‘thought problems’, ‘delinquent behavior’ and aggressive behavior’, or the broad-band scale ‘externalizing problems’. One adolescent obtained a clinical high score on externalizing behavior.

- Insert Table 1 about here -

Self-reports

Virtually all scores of the adolescents on self-report questionnaires did not differ statistically from the norm group (Table 2). The adolescents with ISS or IUGR did not deviate from the norm group with respect to perceived competence and psychological distress. They perceived their ‘social acceptance’ to be even higher than the norm group. With respect to personality characteristics, the adolescents with ISS or IUGR described themselves to be more ‘persevering’ relative to the norm group. Two adolescents obtained a clinical low score (deviation of more than two standard deviations) on global self-worth. One adolescent obtained a clinical high score on trait anxiety.

- Insert Table 2 about here –
Cognitive Functioning

Intelligence scores (IQ) ranged from 66 to 128 (corrected total WISC scores), with an average intelligence of 99.8. Six adolescents had an IQ lower than 80: three adolescents with ISS and three adolescents with IUGR. All parents, except one, reported that their children enjoyed school. According to the parents, 75.5% of the children had adequate school competence and cognitive abilities.

Moderators of motives

With respect to potential moderators (risk or protecting factors) of psychosocial functioning, WISC Total IQ was inversely correlated with ‘perseverance’ (NPV-J) ($r = -0.364, p = 0.037$), and ‘social problems’ (CBCL) ($r = -0.376, p < 0.040$). Age, deviation of height compared to norms, and who had brought about medical referral (family physician, school physician, or pediatrician) were not related to psychological functioning as reported by adolescents and parents. None of the psychological measures demonstrated differences between boys and girls or between the adolescents who would receive hormone treatment and those who would not. Also no differences were found between adolescents with ISS and those with IUGR. This justifies the combining of the two groups in analyses.

Expectations of hormone treatment: perception of current and future height

Perceptions of current and future height were analyzed separately for treatment and control group (Table 3). Most parents and adolescents in the treatment group and in the control group estimated the current height of the adolescent on the 3rd percentile (P3) of population references, which draws nearest to the real height. The parents of the adolescents in the treatment group expected their children to gain more height than the parents of the adolescents in the control group ($Z = -2.68; p = 0.007$).
Groups classified according to motives

Four groups of adolescents were distinguished based on the presence of height related stressors, parental worries about future chances, parental worries about their child’s behavior, and self-reported problems in psychosocial functioning (Table 4).

The first group consists of 4 adolescents and their parents (12%) who did not report any psychosocial problem. However, in this group all adolescents reported to have high expectations of the treatment in terms of gain of height (data not shown).

The second group includes 11 adolescents (32%) whose parents reported height related psychosocial stressors or worries about future chances. Neither the parents nor the adolescents reported problems in psychosocial functioning.

The third group consists of 11 adolescents (32%), whose parents reported problems in psychosocial functioning as well as worries about future chances and in most cases presence of height-related psychosocial stressors. The adolescents themselves did not report problems in psychosocial functioning.

The fourth group consists of 8 adolescents (24%), who themselves reported problems in psychosocial functioning, while their parents did not report height-related psychosocial stressors and worries about future chances, and in most cases did not report behavioral problems.
DISCUSSION

In a medically referred group of early pubertal adolescents with idiopathic short stature or intrauterine growth retardation, the motivation of the adolescents and their parents for hormone treatment was investigated before initiating a combined growth hormone and puberty delaying hormone treatment.

Parental reports revealed that current height-related psychosocial stressors were not a main reason for wanting growth enhancing hormone treatment. Part of the parents reported their children to be teased (28%) or juvenilized (14%) because of their stature. This is close to findings in another Dutch study [8], but in contrast with an American study that showed 50% to be teased and 70% to be juvenilized [15]. The majority of the adolescents was relatively free of current stressors according to their parents. However, more than 40% of the parents expected that their children would have a smaller chance to find a partner or proper job when grown up. Our results suggest that the motivation of providing opportunities for the future of the adolescents constituted for parents a more compelling reason to choose hormone treatment than current negative consequences of the short stature.

Another possible reason for wanting hormone treatment might be worries about psychosocial functioning. On average, as judged by their parents, the adolescents encountered internalizing symptoms, such as anxious or depressed tendencies, as well as social and attention problems. These problems were of a modest magnitude. The adolescents’ perceptions of their own psychosocial functioning did not confirm the parental worries. The adolescents reported normal competence and personality, even higher competence on social acceptance and perseverance, and little distress. This raises the question whether the adolescents or their parents are the best judges about well-being and functioning of the adolescents. The adolescents may fail as informants because they are too young to give an
adequate assessment of their own functioning, lack a time perspective, or are sensitive to denial, while parents may fail because of unrealistic anxieties about their child’s health, future, and behavior. A tendency, that was not confirmed by our data is that children tend to be somewhat more pessimistic than their parents [29, 30]. Our observation of more psychosocial problems reported by parents than adolescents suggests that the perception of psychosocial problems is a stronger motive for parents than for adolescents to participate in the hormone treatment trial.

The results provide some confirmation that intelligence may protect against social suffering as a consequence of short stature. Other factors that were expected to be potential moderators of psychosocial suffering (age, height, medical referral) were not related to psychosocial functioning. This may be due to the low power of our study. Our sample size was large enough to draw conclusions regarding the comparison with normative data, but to examine multiple risk and protective factors a sample size of 49 is required for being able to decide that a moderate correlation of 0.30 is statistically significant [31]. A larger sample size is needed to examine the hypothesis that the combination of multiple risk and protective factors modulates psychosocial functioning of these adolescents.

Our analysis showed four rather mixed profiles of motives for hormone treatment in the adolescents and their parents. In a small group neither the adolescents nor their parents reported psychosocial problems. High treatment expectations of the adolescents in terms of gain of height was the only motive that could be detected. It remained unclear why this group was motivated by the availability of treatment to increase height. Perhaps it predominantly reflects the developmental wish of any child to want to grow (up). For a majority of adolescents the parents reported height-related stressors or psychosocial problems and in most cases these worries about current problems were accompanied by worries about future chances. A final group consisted of adolescents who themselves reported problems in
psychosocial functioning, while their parents not necessarily observed problems and were not worried. The cause of these problems and the relation with height remained unclear. While choosing such an intensive hormone treatment with daily injections, pubertal delay, and possible side-effects, we would have expected at least a subgroup of cases showing a motive in parents as well as adolescents. However, only two parents and adolescent were congruent with respect to the observation of psychosocial problems, and not a single adolescent obtained a score at all motives. In the majority of cases either the parents or the adolescents showed a motive.

**CONCLUSIONS**

Our study demonstrates that the motives of parents to let their children participate in a growth enhancing hormone trial are more clear than the motives of the early pubertal adolescents themselves. Two out of three parents report worries about the future opportunities or observe modest current psychosocial problems of their children. Few adolescents experience psychosocial problems. They want to gain height, but the underlying motivation for this wish remains unclear. Our analyses clearly showed individual differences in terms of motives. This implies that in a proper evaluation of the hormone treatment, different outcome variables are differently important for the different individuals. Perhaps especially the observed psychosocial problems could also be approached with psychosocial counseling. Effectiveness evaluations of the hormone treatment to solve the problems and fulfill the divergent expectations must be awaited.
LIST OF ABBREVIATIONS

ISS  idiopathic short stature
IUGR  intrauterine growth retardation
GH  growth hormone
GnRHa  gonadotropin releasing hormone agonists
CBCL  Child Behavior Check List
SAT  Silhouette Apperception Technique
CBSK/A  Dutch form of Self Perception Profile for Children/Adolescents
ZBV-K  Dutch form of Stait-Trait Anxiety Inventory for Children
KDVK  Dutch Short Depression Questionnaire for Children
NPV-J  Dutch Personality Questionnaire-Junior
WISC-Rn  Dutch short form of the Wechsler Intelligence Scale for Children (Revised)

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS’ CONTRIBUTIONS

HVvB (as first author) and RG carried out the data analyses and the preparation and writing of the manuscript with GS (project supervisor), who was also involved in the study design and acquisition of data as was JH. GK and JMW (medical supervisor) were responsible for the design and execution of the medical part of the study. All authors critically revised the manuscript and read and approved the final manuscript.
REFERENCES


Table 1 Emotional and behavioral problems of adolescents with short stature as judged by the parents

<table>
<thead>
<tr>
<th>Variable</th>
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<th>d</th>
<th>SD</th>
<th>t</th>
<th>p</th>
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<td>Withdrawn behavior</td>
<td>34</td>
<td>0.34</td>
<td>1.10</td>
<td>1.82</td>
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<td>Somatic complaints</td>
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<td>0.38</td>
<td>1.34</td>
<td>1.66</td>
<td>0.11</td>
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<td>34</td>
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<td>2.35</td>
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<td>1.44</td>
<td>2.96</td>
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<td>0.50</td>
<td>1.25</td>
<td>2.35</td>
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Sample sizes (N), mean norm deviation scores (d), standard deviations (SD), t-values, and p-values. The mean norm deviations (d) scores are effect sizes. A value smaller than 0.2 reflects no deviation from the norm, while values between 0.2 and 0.5, between 0.5 and 0.8, and greater than 0.8 reflect small, moderate, and large differences, respectively.

* p < 0.05

** p < 0.01
Table 2. Psychological functioning and distress as reported by the adolescents with short stature.

<table>
<thead>
<tr>
<th>Variable</th>
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<th>d</th>
<th>SD</th>
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<th>p</th>
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<td>0.05 *</td>
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<td>Athletic ability</td>
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<td>0.22</td>
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<td>0.29</td>
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<td>Trait anxiety</td>
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<td>1.07</td>
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Sample sizes (N), mean norm deviation scores (d), standard deviations (SD), t-values, and p-values. The mean norm deviations scores (d) are effect sizes. A value smaller than 0.2 reflects no deviation from the norm, while values between 0.2 and 0.5, between 0.5 and 0.8, and greater than 0.8 reflect small, moderate, and large differences, respectively. * p < 0.05
Table 3 Current and future height as perceived by adolescents and parents on the Silhouette Apperception Technique.

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Treatment group (n = 19) Current height (%)</th>
<th>Control group (n = 19) Current height (%)</th>
<th>Future height (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>adolescents</td>
<td>parents</td>
<td>adolescents</td>
</tr>
<tr>
<td>P3</td>
<td>52.6</td>
<td>88.9</td>
<td>5.3</td>
</tr>
<tr>
<td>P25</td>
<td>36.8</td>
<td>5.6</td>
<td>15.8</td>
</tr>
<tr>
<td>P50</td>
<td>5.3</td>
<td>5.6</td>
<td>26.3</td>
</tr>
<tr>
<td>P75</td>
<td>0.0</td>
<td>0.0</td>
<td>42.1</td>
</tr>
<tr>
<td>P97</td>
<td>5.3</td>
<td>0.0</td>
<td>10.5</td>
</tr>
</tbody>
</table>
Table 4  Classification of adolescents based on motivational forces.

<table>
<thead>
<tr>
<th>Group</th>
<th>Parental reports</th>
<th>Self-reports</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Height related stressors</td>
<td>Worries about future chances</td>
</tr>
<tr>
<td>Group 1 (n=4)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Group 2a (n=3)</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Group 2b (n=4)</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Group 2c (n=4)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Group 3a (n=4)</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Group 3b (n=7)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Group 4a (n=6)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Group 4b (n=2)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
‘+’ indicates presence and a ‘−’ indicates absence of the motive; motives include parental reports of the presence of height related stressors (being teased or juvenilized), worries about future chances (finding a partner or proper job) and behavior problems (internalizing or externalizing), and self-reports of psychosocial functioning (anxiety, low self-worth, or depressive mood); four cases are missing, because one of the classifying variables was missing.