

Auxological screening rules to detect Celiac disease: a case-control simulation study

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Abstract

Background

To study the diagnostic efficiency of several auxological criteria for the detection of children with celiac disease (CD).

Methods

A case-control simulation study was performed. Longitudinal length and weight measurements up to 2.5 years of age from 3 groups of CD patients (one group diagnosed by screening, two groups with clinical manifestations) (n=134) and a reference group obtained from the Social Medical Survey of Children Attending Child Health Clinics (SMOCC) cohort (n=2,151) in The Netherlands were used. The main outcome measures were sensitivity, specificity and positive predictive value (PPV) for each criterion.

Results

The auxological criteria discriminate only poorly between the screened CD group and the reference group. Criteria based on a decrease of Body Mass Index (BMI) performed best for the groups with clinical manifestations. Thirty-four percent of the CD children and 2% of the reference children have a drop in BMI Standard Deviation Scores (SDS) of at least -2.5 per year and a BMI SDS below -1.3 from the age of 0.5 year.

Conclusions

Toddlers with CD detected by screening grow normally. For the symptomatic CD children, the most sensitive auxological parameter is a slowed growth for BMI SDS. BMI is a more important predictor than weight, and much more than length or height.

Background

Growth assessment is accepted worldwide and in many countries regularly integrated in child health care systems.[1] One of the most important goals of growth monitoring in developed countries is the detection of undiagnosed illnesses. There is nevertheless little consensus on referral criteria for children with growth retardation and the diagnostic performance of growth monitoring among countries.[2] Only recently, we reported on the predictive value of various auxological criteria for the detection of Turner's syndrome.[3] Since short stature is the main common physical characteristic of Turner's syndrome, we focused in that study on short stature and slowed growth for length or height. Growth retardation, however, does also imply failure to thrive in terms of slowed growth for weight and BMI.

Celiac disease (CD) is an illness in which both length (or height) deficit and slowed growth for weight might be the earliest signs of the disease. It is a gluten-sensitive enteropathy, characterized by subtotal villous atrophy of the small intestine and may be clinically diagnosed at an early age, when diarrhoea, abdominal distension and/or failure to thrive are present. In the Netherlands in 1994 the incidence of clinically diagnosed CD was 0.54 per 1000 live births.[4] However, CD frequently remains unrecognized. Screening studies by means of detection of anti-endomysium antibodies have shown a much higher prevalence (1:300 to 1:100). The ratio of clinically diagnosed versus screening detected CD is between 1:7 and 1:14.[5] A reduction in adult height, a higher prevalence of malignancies, adverse pregnancy outcome, neurological problems and osteomalacia are associated with CD. Early detection and treatment of CD may prevent these problems.

Mass screening for CD through specific antibodies in the general population probably will not be performed in the forthcoming years because of the uncertainty concerning the cost-benefit ratio. As there is a high incidence of CD (1.7 to 8.3%) in children with growth retardation without gastrointestinal symptoms and even higher (up to 59.1%) when other (endocrine) causes for short stature are excluded [6], a substantial proportion of infants and children with CD may be detected through growth monitoring.

In the Netherlands, nearly every child is monitored for height and weight from birth till the age of 16-18 years. Children with abnormal growth are referred to secondary health care according to certain criteria.[7] As in most of them no pathologic causes for short stature can be detected, we recently revised the referral criteria to minimize unnecessary referrals, without missing important diseases like CD, Turner's syndrome and endocrine diseases.[8]

So far, it is generally assumed that most CD patients have a diminished growth in terms of length (or height) and weight [9], but this is not based on good evidence. This study is a large evidence-based investigation on various types of auxological referral criteria for detecting asymptomatic and symptomatic CD children, aiming at determining optimal auxological referral criteria for detecting CD.

Methods

Material

The longitudinal length and weight data of the patients with CD included in this study were collected from three different studies. The first study was a screening study using blood tests in unrecognised CD in children aged 2-4 years, visiting the Community Child Health Care Centres in the Dutch province of Zuid-Holland.[5] In this study 32 children with CD were detected between May 1997 and June 1998. The second study was a retrospective study on catch up growth in patients with CD.[9] A written questionnaire including their symptomatology, duration of complaints before diagnosis, age at diagnosis, associated diseases in the past and parental heights was sent to all members of the Dutch Celiac Society in the early nineteen eighties. Growth data were collected from 74 children younger than 16 years. The third study was a prospective study on catch up growth.[10] All newly diagnosed childhood CD patients from two separate pediatric departments were included between April 1994 and September 1995 (n=28). We used all growth data before and at the start of the gluten-free diet, till the age of 2.5 years. The data was gathered retrospectively from child welfare clinics, pediatricians and general practitioners. The diagnosis of CD was confirmed by histology for all patients, although in the retrospective study we were dependent on the information provided by patient reports.

The first CD group was prospective (additional data was obtained retrospectively and this data was used) and asymptomatic (or with symptoms that were not signaled by the parents or the general practitioners before) and was therefore analyzed separately (screened group). The second and third symptomatic CD groups were collected retrospectively, and we reasoned that both groups could be pooled (symptomatic group).

A reference sample was obtained from the Social Medical Survey of Children Attending Child Health Clinics (SMOCC) cohort, a nationally representative cohort of 2,151 children born in the Netherlands in 1988-1989.[11] This cohort consists of longitudinal data of length and weight of children up to the age of 2.5 years. Length and weight from birth to two years were previously described by Herngreen et al.[12]

Power analysis

With 134 CD cases we obtain a 95%-C.I. of +/- 8% for an estimated sensitivity of 50% and with the 2,151 reference children a 95%-C.I. of +/-0.6% for an estimated specificity of 98%.

Screening rules

For this study we formulated several auxological rules for screening that could serve as criteria for referral to a specialist care (see table 1). The first rule signals whether an abnormal slowed growth for length/height, weight or BMI occurs in terms of change in standard deviation scores (SDS) per year in combination with a current SDS below some simulation value (*slowed growth rule*). For example, if $e_1 = 0.5$ years, $f_1 = -1.5$ length SDS and $g_1 = -1$ change in SDS per year. Then a child is referred according to this rule if his/her length was measured after or at 0.5 years of age, again his/her length was measured at least 1 month after the first measurement and this length was below -1.5 SDS, and the difference between the second and first length measurement in years was below -1. We prefer the term *slowed growth* over the term *velocity* to indicate the difference in growth in difference in SDS per year as the term *velocity* commonly refers to cm or kg/year. The second rule refers a child based on an absolute change in length/height SDS, weight SDS or BMI SDS occurs (*delta rule*). For example, if $e_2 = 1$ year and $w_1 = -2$ weight SDS, than a child is referred if the second weight measurement is -2 SDS below the first weight measurement

and both weights were measured after 1 year of age (or at 1 year of age for the first measurement). The third rule is the conditional weight gain rule that signals whether a child's conditional weight gain SDS is below some value [13,14] with the restriction of having a low weight SDS (*conditional weight gain rule*). The fourth rule leads to referral of a child if height SDS, weight SDS or BMI SDS is low (*absolute SDS rule*). We also considered rules that take genetic height potential into account. The fifth rule compares the height SDS of the child to its target height SDS in combination with a height SDS below some simulation value (*parental height corrected rule*). The sixth rule signals whether a slowed growth for HSDS of the child moves away from the child's target height (*parental height deflection rule*). This was added because on the assumption that in the first years of life a correction might be needed for parental height: e.g. a baby that is born with a length of -1 SDS and has a target height of +2 SDS, would be expected to cross the SD lines in upward direction in the first 2-3 years. An acquired growth disorder could disturb this, and theoretically a stable length of this child at -1 SDS over the first 2 years could indicate growth pathology such as CD. Similarly, we included a seventh rule that combined weight and length, in which a slowed growth for length occurs after a slowed growth for weight (*combined weight and length deflection rule*).

Several cut-off values for age were used as the effectiveness of these rules may increase by examining higher age groups. Slowed growth requires weights measured at least one month apart. We chose this short time interval to facilitate early detection (less waiting time), taking into consideration that children in the first year of life grow faster than in later years.

It should be noted that some parameters select a subset of the data and assume multiple measurements. The rules were only tested on children that complied with these assumptions. All possible pairs of weights for each infant were used.

Each screening rule was implemented using S-Plus version 7.0, and was applied to the longitudinal data of children. We calculated sensitivity, specificity and positive predictive value (PPV) of different scenarios (a combination of parameters). The rules were ordered according to their sensitivity at high levels of specificity. A higher sensitivity at the same level of specificity, results in a better performance. The graphs are Receiver Operating Characteristic (ROC) curves,

but scaled to different axis in order to view the area of most interest (high specificity). Each point in the ROC curve is the false-positive rate against sensitivity of a scenario (combination of parameters) of a rule. Scenarios of rules with approximately 2% false-positive rate were presented in detail as we assumed that a false-positive rate greater than 2% would result in too many referrals. PPV was calculated, assuming that the average incidence of CD is 0.54 per 1000 live births in the Caucasian population.[4] Sensitivity analyses were performed to calculate the effect of small variations (0.1-1.0/1000) in the incidence of CD on PPV.

Statistical analysis

Length, weight, BMI and weight for length were expressed as SDS, using the Dutch reference growth data.[15][16] In pre-term infants (gestational age < 37 weeks) length and weight SDS were corrected for gestational age. The intrauterine growth charts from the Swedish reference population was used to express SDS till the age corresponding with 40 weeks of gestation.[17] Between 40 and 42 weeks an interpolation between the growth curve of the Swedish reference population and that of the Dutch reference population was used. From 42 weeks of gestation till the age of 2 years, SDS was calculated on ages corrected for gestation, using the Dutch reference growth data.

We assumed that a child was referred if the growth pattern met the criteria of a given screening rule for the first time. All rules were dealt with separately, meaning that the same child could be referred according to each separate rule.

Results

From the 134 children with CD, 12 were excluded from the analyses because of missing data (see figure 1). Table 2 contains general characteristics of the symptomatic CD group and the screened CD group. In the group mean SDS for weight was compromised most, followed by BMI SDS.

We tested the performance of all rules in distinguishing between the CD groups from the reference group. Sensitivity was almost similar to 1-specificity (the false-positive rate) for the group of CD children detected by screening. This indicates that the growth pattern of these patients does not differ much from the reference population. The best screening rule was the

slowed growth for BMI rule that detected 8% of the screened CD children at the account of 2.1% of the reference children.

Figure 2 shows the ROC plots for the four best rules of the symptomatic CD group. Only scenarios with a false-positive rate of less than 10% are plotted. The line for which sensitivity is equal to 1-specificity is given in the figure. Seventeen percent of the CD children and almost none of the reference children had a reduction in BMI SDS of at least -1.5 from the age of 1 year. Thirty-seven percent of the CD children and 3.3% of the reference children had a slowed growth of at least -2.5 BMI SDS per year and a BMI SDS below -1 after the age of 0.5 year.

The properties of the four best rules for the symptomatic CD group, in terms of sensitivity and PPV at approximately 98% specificity, are presented in table 3. Thirty-four percent of the CD children and 2% of the reference children had a slowed growth for BMI SDS of at least -2.5 per year and a BMI SDS below -1.3 from the age of 0.5 year. In children with such slowed growth for BMI SDS the prior-probability of CD (PPV) is 0.86%. PPV varied between 0.16% and 1.59% when changing the incidence of CD from 0.1/1000 to 1.0 per 1000 live births. After 0.5 year of age, 27% of the CD children versus 2% of the reference children had a BMI SDS drop of -1.5. This sensitivity is statistically significant lower than for the slowed growth for BMI rule ($\chi^2(1)=11.9, p<0.001$). Both the conditional weight gain rule as the slowed growth for weight rule results in a sensitivity of approximately 20% at a specificity level of 98%. The difference between this sensitivity and the delta BMI SDS rule was not statistically significant.

The low absolute height rule, rules that take genetic height potential into account (parental height corrected rule and parental height deflection rule) and the combined weight and length deflection rule proved less effective.

Discussion

Our study shows that, as expected, parameters of failure to thrive, such as growth for BMI and weight are better than slowed growth for length or height. Thirty-four percent of the CD children and 2% of the reference children have a drop in BMI Standard Deviation Scores (SDS) of at least

-2.5 per year and a BMI SDS below -1.3 from the age of 0.5 year. The prior-probability of CD (PPV) is 0.86%.

If we assume that the incidence of CD is 0.54 per 1000 live births, then there will be one case of CD in our reference group. Therefore, specificity as well as PPV will be very slightly underestimated

PPV was calculated using the incidence of CD. However, if we keep in mind that children with genetic disorders or diseases other than CD might be detected by some of our rules for failure to thrive, PPV might be higher. For example, if we assume that sensitivity and specificity for the most optimal rule for CD (drop in BMI SDS of at least -2.5 per year and a BMI SDS below -1.3 from the age of 0.5 year) is similar to patients with Cystic Fibrosis (CF), then PPV will be 0.53 percent points higher if this is based on the incidence of both CD and CF.[18]

The used auxological criteria (see methods) discriminate only poorly between the screened CD group and the reference group, which means that these cases grew normally at that specific stage of the disease. However, one might expect that after several years these children would grow worse, as has been documented in children with short stature and no gastrointestinal symptoms investigated for CD, the prevalence being 2-8% [6] compared to a prevalence of 1:300 to 1:100 in the general population.

The conditional weight gain rule corrects for regression to the mean. The amount of regression to the mean depends on the correlation of body weight across age.[13] We took the correlations between the weights from the UK 1990 weight references.[14] To validate if these correlations can also be applied to Dutch children, we calculated if the SDS_{gain} has a mean of zero and a SD of 1, and if it is uncorrelated with the first weight SDS. For the reference group of Dutch children, the mean (SD) SDS_{gain} is -0.06 (1.41) and its correlation with the first weight SDS is -0.23. As both SD and correlation are quite high, the conditional weight gain rule might perform better when using Dutch correlations of weights. Applying these correlations was not possible as these are presently not available. This rule may better discriminate if conditional BMI gain is used, but so far no suitable correlations have been published to calculate this conditional gain.

The CD data in our study were gathered retrospectively, which implies that there was no fixed schedule of measurements, resulting in a wide variation in the number of measurements between the individual patients. We tried to minimize the problem by gathering extra information in the studies cited about growth from school doctors in the Regional health centres, where nearly every child in the Netherlands is monitored for height and weight from birth until the age of 16-18 years.

As Csizmadia et al. reported earlier, the children with CD detected by screening had a normal weight and length at time of diagnosis.[5] We have now shown that all children in this group indeed had a normal growth pattern before diagnosis, which corresponds with the asymptomatic character of this silent form of CD. Thus, auxology seems not useful for the detection of silent CD.

Most of the patients in our study were females, as was reported in several other studies.[19] Bardella et al. hypothesized that males escape diagnosis, but that the two sexes are equally affected. This hypothesis is supported by the absence of differences in gender in the screening study (see table 2).

CD is often atypical or clinically silent and many children remain undiagnosed. However, since the widespread use of serologic testing and the increased awareness of CD in the late 1990s there has been an increase in incidence as well as a change in clinical presentation.[20][21] The classical symptoms, such as malabsorption and poor weight gain, tend to start between the ages of 6-24 months and no longer dominate the clinical picture. Instead, there is an increase of non-classical symptoms such as unusual intestinal complaints or extra-intestinal symptoms such as short stature, involving older children.[22] Since our non-screened population was diagnosed before 1995, we were not able to study the effect of this change in clinical presentation on the performance of the auxological criteria. However, one may assume that for the age-group included in the present study the performance of the auxological criteria is similar for the present CD-population, since it is the delayed onset of the disease (the non-classical form) that has

increased during the recent years, suggesting that the growth impairment becomes apparent much later.

In conclusion, we support the clinician to consider testing for CD in a diagnostic work-up in young children with failure to thrive. The most sensitive auxological parameter is a slowed growth for BMI SDS.

Conclusions

Toddlers with CD detected by screening grow normally at that stage of the disease. BMI is more important than weight, and much more than length or height, to detect symptomatic children with CD.

Competing interests

None declared

Authors' contributions

PvD: Performed statistical analysis and wrote the method and result paragraphs

FKG: Wrote all other paragraphs, acquisition of data

SMPFdMKS Were involved in all versions of the manuscript

BB+GD+CGC: Acquisition of data

JMW+WO+SvB+PHV: Initiated the study, and were involved in all versions of the manuscript

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Figures

Figure 1 - Flow chart of children with CD used in the study

Figure 2 - ROC plots of effective auxological screening rules for detecting CD in the symptomatic group.

The rules are a slowed growth for BMI or weight SDS/year or conditional weight gain in combination with a BMI or weight SDS below some simulation value, and an absolute change in BMI SDS

Tables

Table 1 - Auxological screening rules with their definitions, interpretation of the used parameters and cut off (simulation) values

Table 2 - General characteristics of the CD-population

Table 3 Properties of the best scenarios with approximately 2% false-positives (=98% specificity)

Table 1

Screening rule	Definition	Parameter	Interpretation	Simulation values
Slowed growth *	For ages e_1 to 2.5 years, AND	e_1	Age (in years) after which the rule is effective	0, 0.5, 1
	$X_2 - X_1 \geq 1/12$ refer if		Minimal one month interval between ages X_1 and X_2	
	$SDS_2 < f_1$, AND	f_1	SDS cut off level below which SDS_2 must lie	-1,-1.3, -1.5,-2,-2.5
	$(SDS_2 - SDS_1)/(X_2 - X_1) < g_1$	g_1	Change in SDS per year	-0.5,-1,-1.5,-2,-2.5
Delta-rule*	For ages e_2 to 2.5 years, AND	e_2	Age (in years) after which the rule is effective	0, 0.5, 1
	$X_2 > X_1$ refer if $(SDS_2 - SDS_1) < w_1$	w_1	Change in SDS	-0.5,-1,-1.5,-2,-2.5,-3
Conditional weight gain rule	For ages e_3 to 2.5 years, AND	e_3	Age (in years) after which the rule is effective	0, 0.5, 1
	$X_2 > X_1$ refer if			
	Weight $SDS_2 < f_2$ AND	f_2	SDS cut off level below which SDS_2 must lie	-1,-1.3, -1.5,-2,-2.5
	Weight $SDS_{gain} = (weight\ SDS_2 - r\ weight\ SDS_1)/(\sqrt{1-r^2}) < w_2$	w_2	Change in SDS	-0.5,-1,-1.5,-2,-2.5
Absolute SDS rule*	For ages 0 to e_4 years, refer if	f_3	SDS cut off level before age e_4	-1,-1.3, -1.5, -2,-2.5, -3, -3.5
	$SDS < f_3$, AND	f_4	SDS cut off level after age e_4	-1, -1.3, -1.5, -2, -2.5, -3
	For ages e_4 to 2.5 years, refer if $SDS < f_4$	e_4	Age (in years) at which the referral level changes	0, 0.5, 1
Parental height corrected rule	For ages e_5 to 2.5 years, refer if	e_5	Age (in years) after which the rule is effective	0, 0.5, 1
	Length $SDS < f_5$, AND	f_5	Length SDS cut off level must lie	-1, -1.3, -1.5, -2, -2.5

	Length SDS – TH SDS < g_1	g_1	Difference between length SDS and target height SDS	-1, -1.3, -1.5, -2, -2.5
Parental height deflection	For ages e_6 to 2.5 years, AND $X_2 > X_1$ refer if	e_6	Age (in years) after which the rule is effective Age X_2 after X_1	0, 0.5, 1
rule	(Length SDS ₂ – Length SDS ₁) < w_3 , AND Length SDS ₂ – TH SDS > Length SDS ₁ – TH SDS	w_3	Change in length SDS Length SDS at age X_1 is closer to it's target height than Length SDS at age X_2	-0.5,-1,-1.5,-2,-2.5,-3
Combined weight and length deflection rule	For ages e_7 to 2.5 years, AND $X_3 > X_2 > X_1$, AND $Y_3 > Y_2 > Y_1$, refer if (Weight SDS ₂ – Weight SDS ₁) < w_4 , AND (Length SDS ₂ – Length SDS ₁) < w_5 , AND $Y_1 > X_1$	e_7 w_4 w_5	Age (in years) after which the rule is effective Age X_3 after X_2 , X_2 after X_1 (ages for weight) Age Y_3 after Y_2 , Y_2 after Y_1 (ages for length) Weight velocity change in Weight SDS Length velocity change in Length SDS Starting point length deflection after starting point weight deflection	0, 0.5, 1 -0.25,-0.5,-1,-1.5,-2 -0.25,-0.5,-1,-1.5,-2

* Calculated for length/height, weight, and BMI

Table 2

Characteristic	Screened (n=26)	Symptomatic (n=96)
Gender (M)	50%	35%
Ethnicity		
Dutch	92%	98%
Others	8%	2%
Median (range) age in years at start diet	3.96 (2.94-6.06)	1.43 (0.41-20.7)
Mean (SD) length SDS * ∞	-0.26 (0.98)	-0.89 (1.30)
Mean (SD) weight SDS* ∞	-0.06 (0.81)	-1.54 (1.15)
Mean (SD) BMI SDS* ∞	0.28 (0.57)	-1.28 (1.15)
Mean (SD) weight for length SDS* ∞	0.14 (0.65)	-1.23 (1.13)
Mean (SD) target height SDS	0.41 (0.92)	0.00 (0.75)

* For the children in the screened group figures at diagnosis are given (also when diagnosis is after 2.5 years of age). For the symptomatic CD children figures at the start of diet are given.

∞ Based on children with at least one measurement between 6 months before and 3 months after diet or diagnosis.

Table 3

(symptomatic) CD	Simulation values			Sensitivity	100-Specificity	PPV
Slowed growth for BMI rule	$e_1=0.5$	$f_1=-1.3$	$g_1=-2.5$	33.9%	2.1%	0.86%
BMI delta rule	$e_2=0.5$	$w_1=-1.5$		27.0%	1.9%	0.76%
Conditional weight gain rule	$e_3=0.5$	$f_2=-2.5$	$w_2=-0.5$ to -1.5	20.5%	1.9%	0.58%
Slowed growth for weight rule	$e_1=0.5$	$f_1=-2.5$	$g_1=-0.5$ to -1	19.7%	1.9%	0.56%

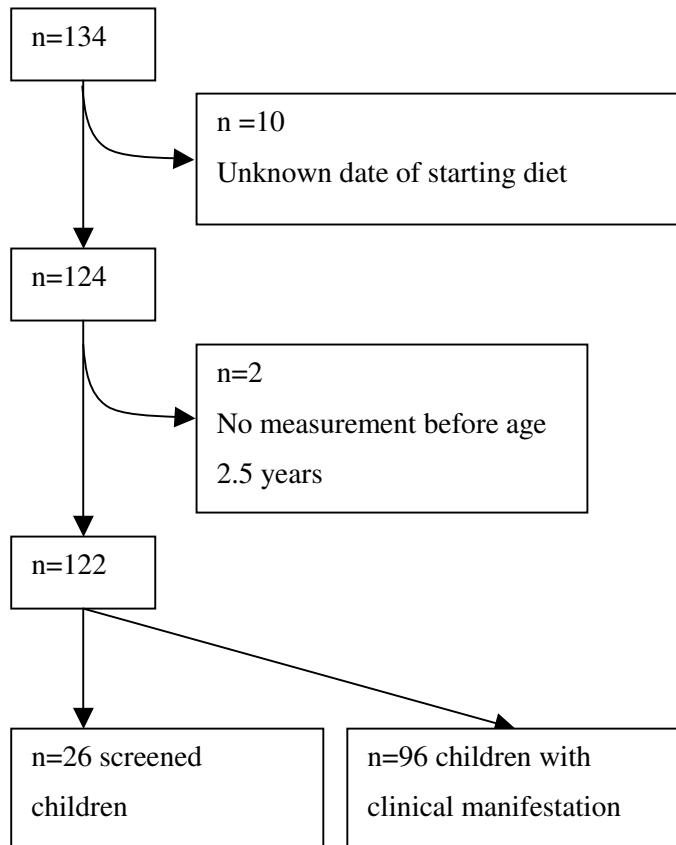


Figure 1

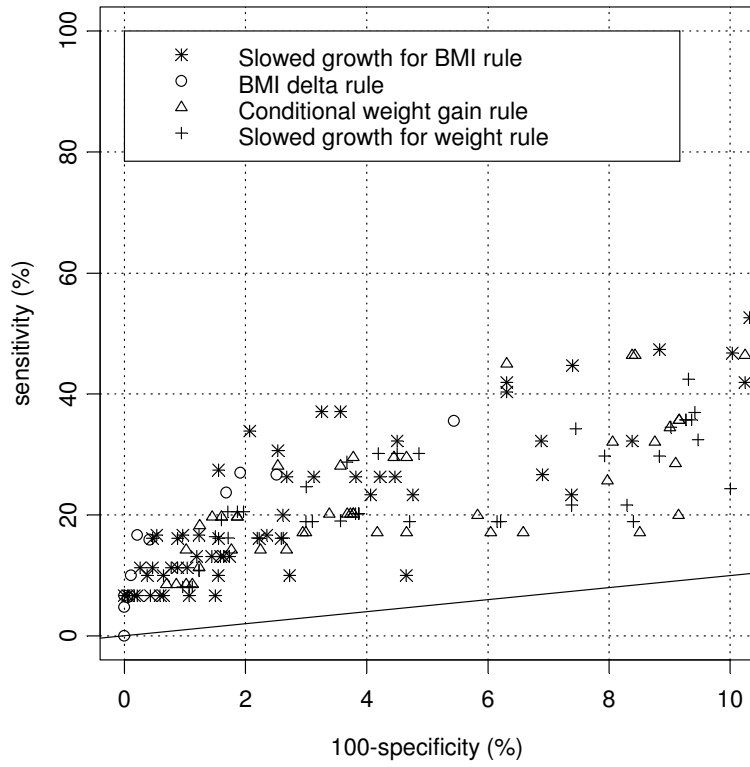


Figure 2