Identifying young children without overweight at high risk for adult overweight: The Terneuzen Birth Cohort

MARLOU L. A. DE KROON1, CARRY M. RENDERS2, JACOBUS P. VAN WOUWE3, REMY A. HIRASING1 & STEF VAN BUUREN3,4

1Department of Public and Occupational Health, EMGO-Institute for Health and Care Research, VU University Medical Centre, Amsterdam, the Netherlands, 2Section of Prevention and Public Health, Department of Health Sciences and EMGO Institute for Health and Care Research, VU University Amsterdam, Amsterdam, 3Netherlands Organisation for Applied Scientific Research, TNO Quality of Life, Prevention and Health Care, Leiden, the Netherlands, 4Dept of Methodology and Statistics, FSS, University of Utrecht, the Netherlands

Abstract
Objectives. To develop a tool to identify children with high risk of adult overweight (AO), especially before developing overweight, based on body mass index (BMI) standard deviation score(s) (SDS) changes between 2–6 years of age.
Methods. We fitted a linear spline model to BMI SDS of 762 young Caucasian adults from the Terneuzen Birth Cohort at fixed ages between birth and 18 y. By linear regression analysis, we assessed the increase in explained variance of the adult BMI SDS by adding the BMI SDS at 2 y to the models including the BMI SDS at 4 y, 6 y and both 4 y and 6 y. AO risk was modelled by logistic regression. The internal validity was estimated using bootstrap techniques. Risk models were represented as risk score diagrams by gender for the age intervals 2–4 y and 2–6 y. Results. In addition to the BMI SDS at certain ages, the previous BMI SDS during childhood is positively related to adult weight. Receiver Operating Curves analysis provides insight into sensible cut-offs (AUC varied from 0.76 to 0.83). The sensitivity and specificity for 2–6 y at the cut-off of 0.25 and 0.5 are respectively, 0.76 and 0.74, and 0.36 and 0.93, whereas the PPV is 0.52 and 0.67, respectively. Conclusions. The risk score diagrams can serve as a tool for young children for primary prevention of adult overweight. To avoid wrongly designating children at risk for AO, we propose a cut-off with a high specificity at the risk of approximately 0.5. After external validation, wider adoption of this tool might enhance primary AO prevention.

Key words: Adult overweight risk, birth cohort, body mass index standard deviation scores (BMI SDS), childhood, prediction tool

Introduction
Overweight and obesity cause serious health hazards (1,2), especially if obesity develops during childhood and is sustained into adulthood (3–6). In young adulthood, not only obesity (Body mass index [BMI] ≥30), but also overweight (BMI ≥25) is associated with a considerable increase in cardiovascular risk (2). The increasing prevalences of overweight and the significantly increased risk for adult overweight in overweight children (7) underline the need for effective prevention programmes. Therefore much attention has been paid to identifying and treating children with overweight. However, the results of treatment for overweight and obesity are disappointing, especially in the long term. Consequently, today’s challenge for Youth Health Care (YHC) is not only to reduce overweight and obesity in childhood, but especially to identify non-overweight children at high risk for developing adult overweight (AO), including obesity, and to offer them primary prevention. It makes sense to consider not only the actual BMI status, but also the change in BMI level, especially in non-overweight children, as this change is an additional risk factor for later overweight (8–10). To enable YHC workers to offer targeted primary prevention to normal-weight children with a high AO risk, a tool to assess this risk is needed. However, no such tool has been developed. Others
have shown that from the age of 2 years (y) onwards abnormally high weight gain is associated with the risk of later obesity, also in normal weight children (11–16). Because overweight at the age of 6 y often translates into overweight in adulthood (17), primary prevention especially before this age seems worthwhile. Moreover, at a young age lifestyle and risk factors of overweight and obesity are easier to modify (18). In a previous study we have shown that the age interval 2–6 y is very sensitive in predicting overweight (19). The aim of our current study is to develop a tool enabling the identification of young children at high risk of adult overweight, based on the BMI changes between 2 and 6 years of age.

**Research design and methods**

**Population and setting**

We analyzed the data of weight and length of 762 Caucasians from the Terneuzen Birth Cohort from birth until young adulthood. The original cohort consists of all 2 604 Caucasian children born between 1977 and 1986 in the city of Terneuzen. Data for weight and length as routinely registered by the Municipal Health Services were available from birth for 1 701 subjects. Of these subjects, 762 persons (45%) were willing to participate in a follow-up study in 2004–2005, when they were between 18 and 28 years of age. This follow-up study included measurements of weight and height and a questionnaire to collect socio-demographic characteristics, which is described in more detail elsewhere (2). The participants in the follow-up study did not differ from the original cohort regarding baseline characteristics, i.e., age, birth weight, BMI standard deviation score (SDS) at birth, and parity and age of the mother, except for gender (41% males vs. 51% in the original cohort p < 0.05). We used BMI values (kg/m²) as the measure for (over)weight, converted to age-specific standard deviation scores (BMI SDS) based on Dutch reference data (20), because these are most comparable to our study population. The criterion for being overweight in young adulthood is defined as BMI ≥25.

The study protocol was approved by the Medical Ethics Committee of the VU University Medical Centre Amsterdam, and written informed consent was obtained from all participants.

**Statistical analyses**

We fitted the so-called ‘broken stick’ model (21) to BMI SDS at fixed ages between birth and 18 y (n = 762), which approximates the observed BMI SDS trajectory of each individual by a series of straight lines that connect to each other at fixed ages (21). Multiple linear regression analysis was applied to assess the proportion of explained variance of the BMI SDS at young adulthood by adding the BMI SDS at 2 y to the models that include the BMI SDS at 6 y, the BMI SDS at 4 y and the BMI SDS at both ages 6 y and 4 y, respectively. Gender and age were analyzed as possible explanatory variables. Gender was analyzed as a potential confounder. Risk of AO was modeled by logistic regression. To test for internal validity, model optimism on the proportion of explained variance, $R^2$, was estimated by the bootstrap procedure, as given by Steyerberg (22), using 1 000 bootstrap samples. In Addendum 1 the statistical methods are explained further. Risk models for AO were graphically represented as risk score diagrams with contour lines, given BMI SDS at the start and the end of the age intervals. For convenience, in the risk score diagrams intended for clinical practice, the axes are labeled by BMI values instead of BMI SDS values. Using Receiver Operating Curves (ROC) analysis we calculated the sensitivity and specificity at various cut-off values for the probability of AO. We used S Plus 8.0 to fit the ‘broken stick model’ and to perform the statistical analyses.

**Results**

The mean age of the participants was 23.1 years (Standard deviation [SD] 2.9), 23.2 years for males (SD 2.9) and 23.0 years (SD 2.9) for females. The prevalence of overweight (BMI ≥25) in young adults was 25.1% for males and 28.4% for females (p > 0.05). Pearson correlations of BMI SDS at the ages of 2 y, 4 y and 6 y, with BMI SDS at adulthood are 0.36, 0.52, and 0.62, respectively (p < 0.001).

**Linear regression analyses**

Because gender appeared to be a confounder, but not an effect-modifier, males and females could be analyzed as one group in the multiple regression analyses (Table I). The proportion of explained variance in the multiple linear regression model of BMI SDS at adulthood as a function of BMI SDS at 4 y increased from 0.28 to 0.34 after extending the model with BMI SDS at 2 y (p < 0.001). Likewise, this proportion increased from 0.39 to 0.47 and from 0.39 to 0.48 by extending the model as a function of BMI SDS at 6 y with the BMI SDS at 4 y and the BMI SDS at 2 y, respectively (p < 0.001). Finally the proportion of explained variance increased from 0.47 to 0.48 by extending the model as a function of BMI SDS at 6 y and 4 y with the BMI SDS at 2 y (p < 0.001), and this proportion remained almost constant, i.e., 0.48, by extending the model as a function of BMI SDS at 6 y and 2 y with the
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All models are adjusted for gender and age.

### BMI SDS at 2 y (p < 0.001).

Therefore, augmenting the model by a second observation obviously improved the prediction of BMI SDS at adult age, whereas the third observation had very little additional value. The positive value of the regression coefficient of the BMI SDS in the models including one BMI SDS increased by adding the BMI SDS at an earlier age, whereas the regression coefficient of the added BMI SDS became negative. This implies, as we showed previously (19), that an increase of BMI SDS in the age intervals is correlated with a higher BMI SDS at adulthood, and a decrease with a lower BMI SDS at adulthood.

#### Logistic regression analyses

Four logistic regression models were fitted. The models incorporate respectively the BMI SDS at 4 y and 2 y, 6 y and 4 y, 6 y and 2 y, and finally, 6 y, 4 y and 2 y. All models except the last one predict significantly better by adding the last mentioned BMI SDS to the model (p < 0.05). Because the last model was of no surplus value in predicting AO in comparison to the second and third model, this model was not elaborated further. Based on the prediction models, it is possible to calculate the AO risk by hand, using the equations of Cole et al. (23), the LMS parameters of the Dutch reference standard of BMI (20) (Table II) and the results of the logistic regression models (Table III). An example of such a calculation is elaborated on in Addendum 2. As shown in this example, it appears that, despite the fact that this boy has a normal BMI at age 6 y, his AO risk is substantial considering the prevalence of overweight of young adult males in this cohort. Similar calculations apply to other pairs of BMI

### Identifying children at risk for adult overweight

Identifying children at risk for adult overweight similar calculations apply to other pairs of BMI

### The risk score diagram and the BMI for age diagram

How are these models related to the conventional BMI diagram? Figure 1a plots the trajectories of five hypothetical children A–E on the Dutch BMI for age diagram. Child A is at low risk and child E at high risk. However, it is not clear how we should distinguish between children B, C and D, who have exactly the same BMI at the age of 6 years. Figure 1b graphs the trajectories for the same children on our risk score diagram. Because the mean age of the cohort is 23.1 years, the risk score diagrams have been developed for 23 years of age. The risk score diagram in this example contains five contour lines, which correspond to 10%, 25%, 50%, 75% and 90% risk values for AO at various combinations of BMI SDS at 2 years and BMI SDS at 6 years. The line through the origin (angle of 45 degrees) consists of all combinations for which the change between the BMI SDS at these two ages equals zero. Children A, C and E are located on this line as their BMI SDS at 2 y is identical to the BMI SDS at 6 y. As expected, child A has the lowest risk of adult overweight and child E the highest. Children located above the main diagonal move upwards through the centiles. Child B increases from -1.0 SD to 0.0 SD (which equals a rise in BMI from 15.0 to 15.5) and has a much higher risk of AO than children C or D, although the BMI (SDS) at the age of 6 years are exactly the same for children B, C and D. According to their risks, the children should be ordered as A, D, C, B, and E.

### Receiver Operating Curves (ROC) analysis, positive predictive value (PPV), sensitivity and specificity

Figure 2a graphs the histogram of AO risk under the girls’ model 2 y 6 y. About half of the girls have a negligible AO risk (P < 0.1). In YHC practice, it is useful to set a cut-off value π on AO risk such that
all children with $P_O \geq \pi$ are eligible for intervention.

A nice property of such a rule is that the PPV of the group of children $P_O = \pi$ is equal to $\pi$. Thus if we set $\pi = 0.5$ and refer those with $P_O \geq \pi$, we expect that at least half of this group will be overweight as an adult. Figure 2b shows how the actual AO prevalence in the eligible group depends on the cut off $\pi$. At $\pi = 0$ the AO prevalence in the eligible group is equal to the prevalence of overweight at young adulthood. Increasing $\pi$ leads to a progressively higher AO proportion in this group, until the remaining group becomes so extreme (at $\pi = 0.82$) that all members fall into the AO group. Occasional drops in AO prevalence occur at $\pi$ values where many subjects with AO are placed. Changing $\pi$ also affects the sensitivity and specificity of the rule. Figure 3 plots ROC under models 2 y 6 y and 2 y 4 y. Model 2 y 6 y is more informative than model 2 y 4 y, i.e., at the same specificity; model 2 y 4 y has a lower sensitivity than model 2 y 6 y. The AUC for the models 2 y 4 y and 2 y 6 y was 0.79 (95% CI: 0.73–0.85) and 0.83 (95% CI: 0.78–0.88), respectively, for boys, and 0.76 (95% CI: 0.71–0.81) and 0.79 (95% CI: 0.75–0.84), respectively, for girls. On the basis of the ROC analyses, the cut-off values for AO risk should be chosen around 0.25. In clinical practice this means that we single out those children with a risk of AO of 0.25 and higher, and subsequently offer them targeted preventive interventions.

In Table IV, the PPV, the sensitivity and specificity of the models are given for different cut-offs on AO risk. At a rising cut-off the PPV rises, the sensitivity decreases and the specificity rises. The percentage (%) of false-positive children can be derived from this Table by calculating ‘1-specificity’, e.g., at a cut-off of 0.25 the % false positive children varies from 26 to 29%, whereas at a cut-off of 0.50, these values vary from 7 to 8%.

The risk score diagrams and general practice

Figures 4 and 5 contain the risk score diagrams for males and females for the age intervals 2–6 y and 2–4 y, respectively, which make it easy to identify children at high risk of AO. The risk score diagrams for the age interval 4–6 y is not given as its practical value seems less obvious. For practical purposes the four risk score diagrams that can be used to estimate AO risk are expressed as a function of BMI instead of BMI SDS. The risk of AO can be read from the contour lines of these diagrams, and is based on the BMI at two ages, of which the BMI at the start of the interval is given by the value on the X-axis, and the end of the interval by the value on the Y-axis. If the child has the BMI at the age that is given on the X-axis, an indication of AO risk can be given for the combination of the BMI on the X-axis and various values of BMI at the age that will be reached as given on the Y-axis.

Discussion and conclusion

We developed a tool to identify children with a high risk of AO and in particular those who are not yet overweight. The tools consist of several risk score diagrams, which are all based on two measurements of the BMI, because including a third did not improve the performance of the tools. The explained variance of adult BMI by the BMI development between 2 and 6 years of more than 40% is considerable, especially taking into account that this age interval concerns a very early growth period in human life and the age interval 2–6 y only covers 22% of the age range between 0–18 years. The BMI changes in the age intervals 2–4 y and 4–6 y contribute equally to AO risk. We have developed risk score diagrams and illustrated the use of these diagrams.

Cut-off values

An indication of a normal growth of a child from 2 years onwards can be extracted from the risk score diagrams. The diagrams show how the BMI should develop to 4 and 6 years of age, respectively, to secure a low AO risk. In addition, the diagram for 2–4 y offers a mid-term estimate of AO risk that could be used to evaluate weight change at the age of 4 y. After an evaluation with the help of the diagram for 2–4 y, the diagram for 2–6 y should be applied to determine
if the BMI development of the child is normal or whether it should be adjusted.

The ROC plots of the risk score diagrams suggest cut-off values for the risk at approximately 0.25. At this cut-off about 30% of the children that did not develop AO are wrongly designated as ‘high risk’. Therefore the choice of a cut-off at 50% seems more sensible because this is associated with only 8% of false positive results. At the cut-off around 0.5, we find that the PPV is 67% of the 2–6-year-old children with an estimated overweight risk of >0.5. Another important consideration in deciding to offer preventive intervention is its cost-effectiveness.

Context of the study results

The prevalence of adult overweight (BMI ≥25) in the Netherlands is still rising: in 2004 it was 51% and 42% for adult males and females, respectively. In addition the prevalences are higher in later birth cohorts and tend to evolve into obesity at older ages (24). Therefore primary prevention of AO is very important in lowering these figures. In addition to interventions targeting the total population of children (universal prevention) it will be particularly efficient to identify children at high risk for developing overweight. Therefore tools are needed that can
be easily incorporated within preventive health care. We developed this tool, which is aimed at the age interval 2–6 y, just before the AR, which is known to be crucial for developing overweight (15,25).

Several studies have assessed the relationship between a relatively fast BMI increase (or upwards centile crossing) between 2 to 5 or 6 years, and adult overweight or obesity (11,15,25,26). One of these studies also constructed risk charts based on serial BMI SDS in a non-Caucasian cohort (26). Moreover, these charts are meant to identify children at risk of the metabolic syndrome and diabetes.

Strengths and limitations

A methodological difficulty of our study is that we had to deal with missing values, which can cause the individual broken stick models to shrink further towards the overall mean. Therefore, any tests of differences will be conservative, and possibly underestimate the effects of BMI changes in age intervals in which fewer measurements are recorded. Another limitation was that as in most cohort studies there was a substantial loss to follow-up (10). Therefore sampling bias might be possible. However, there is no reason to assume that the loss to follow-up is related to the strength of the relationship between BMI changes in childhood and adult BMI. Moreover, no significant differences were found for the baseline characteristics for males and females between those that participated in the follow-up study and the original cohort.

We should be aware that no data on the representativeness of well-known risk factors for overweight, such as socio-economic status, parental weight status and parenting, were available. It is not clear if and how these risk factors influence the performance of the tool. The study population of Terneuzen differs slightly from the total Dutch population regarding e.g., the prevalence of overweight, which was higher in the Terneuzen cohort than in 15–25-year-olds in the general Dutch population in 2006 (27.0 vs. 20.4%) (27), although this difference might be largely due to the age distribution. Therefore cohort effects cannot be excluded.

Because of the above mentioned limitations, the tool should be validated in younger cohorts, before implementing the tool in YHC. This will improve its generalisibility. Beyond validation, adaptations of the tool to other ethnicities or other possible risk factors

Table IV. The positive predictive value (PPV), sensitivity and specificity of the three risk models 2y4y, 2y6y and 4y6y at 23y of age at three different cut-offs.

<table>
<thead>
<tr>
<th>Cut-offs</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV of model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2y4y</td>
<td>0.49</td>
<td>0.58</td>
<td>0.94</td>
</tr>
<tr>
<td>2y6y</td>
<td>0.52</td>
<td>0.67</td>
<td>0.86</td>
</tr>
<tr>
<td>Sensitivity of model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2y4y</td>
<td>0.75</td>
<td>0.28</td>
<td>0.08</td>
</tr>
<tr>
<td>2y6y</td>
<td>0.76</td>
<td>0.36</td>
<td>0.15</td>
</tr>
<tr>
<td>Specificity of model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2y4y</td>
<td>0.71</td>
<td>0.92</td>
<td>1.00</td>
</tr>
<tr>
<td>2y6y</td>
<td>0.76</td>
<td>0.93</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Figure 3. ROC plots of models 2y6y and 2y4y, including the risk of AO at several points. The AUC was respectively 0.83 (95%CI 0.78–0.88) and 0.79 (95%CI 0.73–0.85) for boys (figure a), and respectively 0.80 (95%CI 0.75–0.84) and 0.76 (95%CI 0.71–0.81) for girls (figure b).
Identifying children at risk for adult overweight might be necessary. It is to be expected that the PPV of the tool will increase in younger birth cohorts as the higher prevalences of AO in younger cohorts will be in favor of the PPV of the tools. Also, we should realize that BMI at young adulthood possibly underestimates ultimate adult obesity (24). However, by developing a tool aimed at the risk estimation of overweight (including obesity) at young adulthood, this tool will probably also predict the more severe cases of overweight at later adulthood.

A limitation of the risk score diagram as presented is that it will only work if the children have been measured at two specific ages. Figure 4 shows the risk score diagrams for boys measured at ages 2 y and 4 y, as well as the risk score diagrams for boys measured at ages 2 y and 6 y. Figure 5 demonstrates the same for girls.

Figure 4. (a) Risk score diagram for boys measured at ages 2 y and 4 y; (b) Risk score diagram for boys measured at ages 2 y and 6 y.

The risk on adult overweight (AO) at 23 years of age (in %) can be read from the contour lines of these diagrams, and is based on the body mass index (BMI) at two ages, of which the BMI at the start of the age interval is given by the value on the X-axis, and at the end by the value on the Y-axis. If the child has approximately the age as given on the X axis, an indication of AO risk can be given for various values of BMI at the age which will be reached as given on the Y axis.

Figure 5. (a) Risk score diagram for girls measured at ages 2 y and 4 y; (b) Risk score diagram for girls measured at ages 2 y and 6 y.

The risk on adult overweight (AO) at 23 years of age (in %) can be read from the contour lines of these diagrams, and is based on the body mass index (BMI) at two ages, of which the BMI at the start of the age interval is given by the value on the X-axis, and at the end by the value on the Y-axis. If the child has approximately the age as given on the X axis, an indication of AO risk can be given for various values of BMI at the age which will be reached as given on the Y axis.
measured at ages 2 y, 4 y and 6 y. As long as the age of the measurement does not differ substantially from the target by no more than 2–3 months, the risk score diagrams will remain valid, especially if the length of the age intervals remain close to two or four years.

Finally, because BMI SDS reflects total body mass and not body fatness, it might be possible that a relatively high BMI increase during the age interval 2–6 years is also due to an increase in muscular and bone tissue. Therefore future research should take into account the predictive value of waist circumference or, less known, neck circumference at childhood, both strongly related to the risk of cardiometabolic diseases (11,28,29). However, the BMI is still the most common measurement used to estimate body fat. Moreover, several studies have shown that an early AR, which is the result of upwards centile crossing of the BMI just before the age of 6 years (30), is caused by a rapid elevation in the deposition of body fat rather than lean tissue mass (25).

The strength of our study is that we have developed a tool suitable for primary prevention for children who are not yet overweight. Two-dimensional easy-to-use risk score diagrams could be developed, because adding a third BMI SDS to the model did not significantly improve the performance of the model. The accepted definition of overweight in children is based on the cut-off values of the International Obesity Task Force (IOTF), centile curves with variable cut-off values for different ages (31). However, the risk of AO at the IOTF cut-offs increases with age. Therefore preventive interventions that are offered to children with a BMI above the IOTF cut-off point for overweight may have, depending on age, quite different implications for future weight. The advantage of the methodology proposed in this paper is that it provides an alternative that is directly based on risk of AO. Because the tools take both the actual BMI SDS and BMI SDS change into account, the new approach could lead to different interventions for children of the same age and same BMI.

Relevance and usefulness within the setting of the Youth Health Care (YHC)

In the Netherlands, the tool might be used within YHC that reaches more than 90% of all Dutch infants from birth onwards by a nationwide program at set ages (32). During the YHC check-ups the length and weight of each child are measured. Based on the information in the risk score diagrams (Figures 4 and 5), parents can be given information and an indication about the risk of AO, and thereby be advised about the preferred growth and nutrition of their child until the ages of 4 y and 6 y. This also applies to parents of children who are already overweight at 2 y or 4 y, so they can be motivated to modify the family’s and children’s lifestyle to prevent AO. Within YHC it might also be considered to use the tool selectively for those children with a high risk of overweight, which can already be assessed before the age of 2 years, e.g., by assessing risk factors, such as the BMI of the parents, ethnicity, or SES (33–35).

Tailored primary prevention programs might be offered to these high-risk children, aimed at e.g., stimulating breastfeeding, daily physical activity, and eating breakfast, and preventing the watching of television and drinking of sweetened beverages.

Conclusion

Our tool can support preventive healthcare professionals in the early detection of young children at high AO risk with the aim of deciding as to whether or not tailored preventive interventions should be offered. Moreover, the tool can be used as an instrument for primary prevention by informing parents about the risks of upward centile crossing during the age interval 2–6 y. The feasibility and effectiveness of the tool in combination with offering tailored preventive interventions should be studied, e.g., in ongoing trials. After external validation and a positive evaluation of related interventions, a wider adoption of this tool might enhance primary prevention of overweight during a very sensitive period in human growth.

Acknowledgements

This study received a grant from the Health Research and Development Council of the Netherlands (ZONMw Grants no. 2100.0092). The researchers are not dependent on the funder. We gratefully thank all participants for their time and efforts, the assistants for their contribution to the research, the Municipal Health Services of Terneuzen (GGD Zeeland) for their support and cooperation, and Guus A. de Jonge, PhD, professor emeritus, for laying the foundations of this study in 1977–1986.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

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10. Fall CH, Sachdev HS, Osmond C et al. Adult metabolic syndrome and impaired glucose tolerance are associated with different patterns of body mass index gain during infancy; Data from the New Delhi birth cohort. Diabetes Care. 2008;31:2349–56.


Supplementary material available online

Addendum 1

Addendum 2