Metabolic status in children and its transitions during childhood and adolescence - The IDEFICS/I.Family study

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Metabolic status in children and its transitions during childhood and adolescence - The IDEFICS/I.Family study

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Abstract (254/250 words)

Background: This study aimed to investigate metabolic status in children and its transitions into adolescence.

Methods: The analysis was based on 6768 children who participated in the European IDEFICS/I.Family cohort (T0 2007/2008, T1 2009/2010 and/or T3 2013/2014; mean ages: 6.6, 8.4, and 12.0 years, respectively) and provided at least 2 measurements of waist circumference, blood pressure, blood glucose and lipids over time. Latent Transition Analysis was used to identify groups with similar metabolic status and to estimate transition probabilities.

Results: The best-fitting model identified 5 latent groups: 1. metabolically healthy (61.5%; probability for group membership at T0), 2. abdominal obesity (15.9%), 3. hypertension (7.0%), 4. dyslipidemia (9.0%), 5. several metabolic syndrome (MetS) components (6.6%).

The probability of metabolically healthy children at T0 to remain healthy at T1 was 86.6%; when transitioning from T1 to T3 it was 90.1%. Metabolically healthy children further had a 6.7% probability of developing abdominal obesity at T1. With a probability of 18.5%, children with abdominal obesity at T0 developed several MetS components at T1. The subgroup with dyslipidemia at T0 had the highest chances of becoming metabolically healthy at T1 (32.4%) or at T3 (35.1%). Only a minor proportion of children showing several MetS components at T0 were classified as healthy at follow-up; 99.8% and 88.3% remained in the group with several disorders at T1 and T3, respectively.

Conclusions: Our study identified five distinct metabolic statuses in children and adolescents. While lipid disturbances seem to be quite reversible, abdominal obesity is likely to be followed by further metabolic disturbances.

Key messages

- Latent transition analysis is a powerful tool to identify groups of children with distinct metabolic status and to estimate changes in metabolic status over several years
- Five distinct metabolic statuses were identified in children and adolescents
- Lipid disturbances can be quickly reversed during childhood or adolescence whereas abdominal obesity is likely to be the trigger for further metabolic disturbances
- Puberty is a window in time during which the risk for developing of metabolic abnormalities increases

Background

Chronic diseases such as cardiovascular diseases (CVD), cancer and type 2 diabetes are among the top causes of death and represent a major burden for our quality of life.[1] Before chronic diseases become manifest, typically several risk factors occur and accumulate, in particular abdominal obesity, hypertension, dyslipidemia and impaired glucose tolerance, and a triad of them is summarized as metabolic syndrome (MetS).[2,3] Accumulation of these risk factors is not only seen in adults but already in young children and adolescents.[4,5] Recently, based on the large European IDEFICS (Identification and Prevention of Dietary- and Lifestyle-Induced Health Effects in Children and Infants) cohort, a new definition for the MetS has been suggested based on reference values derived for children.[6] In this previous investigation of mainly prepubertal children, a prevalence of the MetS of 0.4 to 5.5 % was observed in the total population increasing up to 31.5% in obese children depending on the definition used.[6] Similar prevalence of MetS and incidence of cardiovascular risk factors have been reported in other children cohorts.[5,7] Previous studies have shown that temporal changes in metabolic risk factors already occur in early adulthood, years before the onset of clinical CVD events.[8,9] However, in children little is known about the temporal occurrence of the components of the MetS and the chances of their remission over time. This would require large cohorts of children with multiple examinations and blood sample collections, which are scarce due to ethical and cost constraints. Children represent an important target group as metabolic risk factors are not yet as manifest as in adults and may potentially be reversed more easily.

Also from a methodological perspective, it is challenging to assess the clustering of metabolic risk factors and its progression over time due to the variety of possible

combinations of risk factors (16 combinations of showing/not showing the four MetS components plus respective changes over time). Some risk factor combinations will occur only rarely leading to estimation problems with respect to these sparse groups. Latent class analysis (LCA) helps to reduce the dimensionality of data in such situations by identification of groups of subjects with distinct status with respect to the variables considered.[10] Latent transition analysis (LTA) is a longitudinal extension of LCA that enables the estimation of transition probabilities among latent statuses over time.[10] To the authors' knowledge, no study to date assessed the metabolic status in children and its transitions during childhood and adolescence using this sophisticated statistical method.

Therefore, the present study aims (1) to identify groups of children with distinct metabolic status and (2) to estimate the probabilities of changes in metabolic status when transitioning into adolescence. For this purpose, LTA will be applied to the large and well-phenotyped IDEFICS/I.Family cohort which provides unique longitudinal data in European children and adolescents from multiple examinations and blood sample collections over time.

Methods

Study population and data

The IDEFICS /I.Family cohort is a multi-centre population-based study aiming to investigate and prevent the causes of diet- and lifestyle-related diseases in children and adolescents.[11] Participants were aged 2 to <10 years at the baseline survey (T0) that was conducted from September 2007 to May 2008 in eight European countries (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain, Sweden). In total, 16 229 children participated and fulfilled the inclusion criteria. The baseline examination

included interviews with parents concerning lifestyle habits and dietary intakes as well as physical examinations of the children. Details can be obtained from Ahrens et al.[12,13] A follow-up examination (T1) was conducted in 2009/2010 applying the same standardized assessments where 13 596 children were enrolled (2555 newcomers; 11 041 (68%) children who had participated in T0). A second follow-up examination (T3) took place in 2013/2014 where again 7105 (44%) out of the children participating already in T0 or T1 were included.[11] A detailed description of all study measures used in the present analysis is given in Supplementary Material S1. Before children entered the study, parents provided written informed consent. Additionally, children 12 years and older gave simplified written consent. Younger children gave verbal assent for examinations and sample collection. Ethical approval was obtained from the institutional review boards of all eight study centres.

Metabolic syndrome components

As levels of many health parameters change during childhood, a new definition of MetS and of disturbances in its single components has been proposed by Ahrens et al.[6] for children which was applied in the present analysis. According to previously described methods[14-17], sex- and age-specific reference values were derived for waist circumference, diastolic and systolic blood pressure (also height-specific), high-density lipoprotein-cholesterol (HDL-C), triglycerides and blood glucose in children and adolescents using the data collected in the IDEFICS/I.Family cohort. In case the measurement method changed over time, separate reference curves were estimated depending on the assessment method used (applies to blood glucose, HDL-C and triglycerides; see Supplementary Material S1). Subsequently, children were defined as being above the so-called “monitoring” or “action” levels of the different metabolic parameters, in case the parameters exceeded the 90th or 95th age- and sex-specific

reference percentiles (age-, sex- and height specific in case of blood pressure), respectively. In the present investigation waist circumference was considered as a marker for abdominal obesity, systolic (SBP) and diastolic blood pressure (DBP) for hypertension (criterion: either SBP or DBP above 90th/95th percentile, respectively), triglycerides and HDL-C for dyslipidemia (criterion: either triglycerides above 90th/95th percentile or HDL-C below 10th/5th percentile) and fasting blood glucose as marker for impaired glucose tolerance.

Pubertal status

At T3, pubertal status (yes vs no; yes if menarche had already occurred in girls or if voice alterations had already started/ were completed in boys) was self-reported by children 8 years and older based on questions adapted from Carskadon and Acebo.[18]

Analysis dataset

Our analysis dataset included all children in the age range from ≥4 to ≤15 years across all waves providing at least two repeated measurements of all MetS components (waist circumference, blood pressure, blood lipids and blood glucose). Laboratory measurements obtained based on non-fasting blood samples were not considered (N=1897 measurements) as well as children taking medications that may influence our parameters of interest. For the latter purpose, children being treated for type1/type2 diabetes (ATC codes: A10A, A10B, A10X), elevated blood lipids (C10), hypertension (C02, C03, C07, C08, C09) or obesity (A08) were identified based on ATC codes of reported medications and excluded (N=54). This led to a final study sample of 6768 children.

Statistical methods

Applying the above definition, variables were derived indicating children “with normal levels”, “above monitoring levels (P90)” and “above action levels (P95)” with respect to the four metabolic markers (waist circumference, blood pressure, lipid levels, blood glucose). Based on these variables, LTA[10] was conducted to identify groups of children with distinct metabolic statuses (latent groups) and to estimate (a) probabilities (prevalence) for latent statuses at T0, T1 and T3, (b) probabilities for transitions between latent statuses from T0 to T1 and T1 to T3 as well as (c) item-response probabilities conditional on latent status membership (i.e. probabilities of showing normal levels or levels above the monitoring or action levels for the metabolic markers in the different latent statuses). Further details on the statistical analyses are given in Supplementary Material S2.

Models with 3 up to 7 latent statuses were estimated with the 5-status model showing the best fit (evaluated based on the Bayesian Information Criterion (BIC)).

LTA was conducted for the total study sample as well as stratified by sex and age (2-<6 vs 6-<10 years at T0) and separately for children who had entered puberty at the time of the T3 examination.

All analyses were performed using SAS® statistical software version 9.3 (SAS Institute, Inc., Cary, NC, USA). Proc LTA was used to conduct the LTA.

Results

A description of the study population and study measures is provided in Table 1 and 2. Mean ages of children at T0, T1 and T3 are 6.6 years, 8.4 years and 12.0 years,

respectively. Mean values of all MetS components increase as children get older (i.e. are highest at T3).

(Table 1 and 2 here)

At T0, 26.0% of the children fall above the monitoring or action level for abdominal obesity with the percentage rising up to 30.9% and 32.1% at T1 and T3, respectively (see Table 2). Prevalence of the other components of the MetS falling above the monitoring or action levels are 19.2% for blood pressure, 17.0% for blood lipids and 16.2% for blood glucose at T0. Waist circumference is not only the most common risk factor at all measurement points but also occurs most often in combination with the other risk factors (see Supplementary Material S3 showing prevalence of all risk factor combinations over time).

Results of the LTA

The identified latent groups are characterized as follows (see Table 3): Children in group 1 show a high probability of being within the normal range of all metabolic markers (all above 87.2%; labeled as “metabolically healthy”). In group 2, labeled as “abdominal obesity”, the probability of having normal levels for waist circumference is only 5.8% but high for the other metabolic markers. Group 3 is characterized by a low probability of having normal blood pressure (17.8%; labeled as “hypertension”) whereas in group 4, the probability of having normal lipid levels is low (24.6%; labeled as “dyslipidemia”). Finally, in group 5, the probability of having normal waist circumference is almost zero (0.7%) and also probabilities of normal levels for the other metabolic markers are rather low (max. 55.2%; labeled as “several MetS components”). No group of children is identified suffering mainly from glucose disturbances.

(Table 3 here)

Probabilities of being assigned to the different latent groups at T0, T1 and T3 are shown in Table 4. Children have the largest probability of being classified as metabolically healthy (61.5% at T0, 56.5% at T1 and 59.8% at T3) whereas the probabilities are lowest for having dyslipidemia or hypertension (below 10%). At T0, T1 and T3 the probabilities for children to have abdominal obesity are 15.9%, 17.2% and 18.0%, respectively, i.e. increasing over time. Also the probabilities of showing several MetS components are markedly higher at T1 (10.5%) and T3 (12.1%) compared to T0 (6.6%). Supplementary Material S4 shows age, sex and body mass index (BMI) distributions with regard to the different metabolic statuses. Both, mean age and BMI (z-score), are highest in the group showing several MetS components followed by the abdominal obesity group.

(Table 4 here)

Transition probabilities for changes in metabolic status from T0 to T1 and from T1 to T3 are displayed in Table 5, Figure 1 and 2 as well as in Supplementary Material S5 to S7. The probability of metabolically healthy children at T0 to remain healthy at T1 is 86.6%; when transitioning from T1 to T3 it is 90.1% (see Figure 1). Metabolically healthy children at T0 further have a 6.7% probability of switching to the abdominal obesity group at T1 and 7.2% at T3, respectively. Children with abdominal obesity at T0 show a probability of 18.5% to develop several MetS components in T1 (see Figure 2) as opposed to only 0.7% for those who were metabolically healthy at T0. Out of all children with any metabolic disturbances, the subgroup of children with dyslipidemia at T0 has the highest probability to become metabolically healthy (32.4% at T1 and 35.1% at T3; see Table 5 and Supplementary Material S5). Children with hypertension at T0 show a 92.2% probability of remaining hypertensive

at T1; when transitioning from T1 to T3 the probability of hypertensive children is 40.3% to become metabolically healthy. Finally, children with several MetS components at T0 remain with a probability of 99.8% in the same group at T1. With regard to the transition from T1 to T3 the probability is still 88.3% being the most stable pattern over time followed by the metabolically healthy group.

(Table 5 and Figures 1,2 here)

***[Figure 1:** Transition probabilities from T0 to T1 as well as from T1 to T3 of children being in the metabolically healthy group (61.5% at T0)*

Figure 2:** Transition probabilities from T0 to T1 as well as from T1 to T3 of children being in the abdominal obesity group (15.9% at T0)]**

We observed only negligible differences between males and females (data not shown). However, results differ markedly by age group (< 6 years at baseline vs ≥ 6 years at baseline; see Supplementary Material S8). Especially the percentage of children with several MetS components is much higher in older children compared to the younger ones at all three time points but increases from T0 to T3 in both, younger and older children. The proportion of children with several MetS components is highest in children that have entered puberty at T3 (see Supplementary Material S8). The results of several sensitivity analyses are presented in Supplementary Material S9.

Discussion

In the present study we identified five distinct metabolic statuses among children of the IDEFICS/I.Family cohort, namely “metabolically healthy”, “abdominal obesity”, “hypertension”, “dyslipidemia” and “several MetS components”. Over time, particularly the prevalence of abdominal obesity and of showing several MetS

components increased; and these two statuses were less likely to be reversed to the metabolically healthy status.

For metabolically healthy children at baseline, the highest risk is to develop abdominal obesity, followed by dyslipidemia, while risks for developing hypertension or several MetS components are very small. This may indicate that (abdominal) obesity is indeed the starting point for subsequent metabolic disturbances. Our observation is in line with the Framingham Heart Study which reported the presence of abdominal obesity to be the main risk factor for the development of MetS in adults.[19] In another adult cohort it was observed that particularly an increase in BMI and decrease in HDL-C preceded the onset of type 2 diabetes.[8] Recent studies in children and teens also suggest unfavorable weight development to be associated with subsequent adverse cardiovascular profiles.[20-22]

Among children with abdominal obesity who changed their metabolic status over time, the largest proportion either developed several MetS components or became metabolically healthy. Lipid disturbances on the other hand seem to be quite reversible as approximately one third of the children in that group became metabolically healthy at T1 and T3. Indeed, previous studies reported that increased triglycerides were more prevalent in 0 to 9 than in 10 to 16 year old children[23] and the median triglyceride concentration decreased gradually in Korean girls from the 11-year-old age group to the 19-year-old age group.[24] Additionally, studies have shown that lifestyle modifications substantially improved blood lipid levels already in the short-term.[25,26] Thus, blood lipid levels may change more easily as compared to other metabolic markers when entering youth.

In general, few children suffered solely from dyslipidemia or solely from hypertension. This observation underscores the hypothesis that lipid disturbances or hypertension

rarely occur in isolation but are more likely to manifest as a comorbid condition of abdominal obesity. Exclusive abdominal obesity indeed appears in a substantial proportion of children and may hence present the starting point for the other metabolic disorders. A distinction between metabolically healthy and metabolically unhealthy obesity has been suggested, but is poorly understood in children.[27] This concept is further discussed controversially as previous studies have shown that the majority of metabolically healthy obese progress to an unhealthy status.[28,29] Thus, metabolically healthy obesity may just be considered as an intermediate state in the development of MetS.[28,30] Nevertheless, increased abdominal fat tissue was shown to be associated with the metabolically unhealthy obese phenotype.[27,31] Several mechanisms are discussed indicating that the characteristics of abdominal adipose tissue can vary and may differently influence metabolic health.[31] Obesity per se may directly raise blood pressure through different pathways, such as adversely affecting intravascular volume, cardiac systolic and diastolic function and output, as well as renal-pressure natriuresis and renal medullary compression.[32] In addition, obesity may induce dyslipidemia particularly through elevated fasting and postprandial triglycerides, partly caused by increased flux of free fatty acids to the liver.[33] Hypertriglyceridemia then further causes delayed clearance of the triglyceride-rich lipoproteins, which eventually leads to low levels of HDL-C as well as high levels of pro-atherogenic small dense LDL-particles.[33]

No latent status was found that was mainly characterized by glucose disturbances. When estimating the LTA with 6 groups, the additional group was indeed characterized by children showing a high probability for glucose being above the monitoring or action level (data not shown). However, the probability for group membership was very small (1.9% at T0) and the model fit worse compared to the selected 5-group model. Our results suggest that glucose disturbances mainly go

253 along with obesity and are rarely present in children not suffering from additional
254 metabolic disturbances. This is in line with previous studies suggesting that insulin
255 resistance and obesity typically co-exist being integral in the development of multiple
256 metabolic disturbances.[34,35] There is some evidence that insulin resistance may even
257 be causally involved in the development of obesity.[36] However, the majority of
258 literature suggests the reverse direction, i.e. obesity to cause insulin resistance.[37-42]
259 The excessive adipose tissue may lead to an increased flux of free fatty acids and
260 dysregulated adipokine secretion including lower secretion of insulin-sensitizing
261 adipokines such as adiponectin and upregulated secretion of proinflammatory
262 adipokines.[43] These mechanisms may trigger insulin resistance.
263 Another observation in the present study was that probabilities for changing the
264 group were higher when transitioning from T1 to T3 compared to the transition from
265 T0 to T1 (except for the metabolically healthy group). This may be either explained
266 by the longer follow-up time (approx. 2 years from T0 to T1 and approx. 4 years from
267 T1 to T3) but also by the fact that the time period from T1 to T3 goes along with
268 entering puberty in approx. one third of our children (N=1830). Puberty incorporates
269 various hormonal and body changes including puberty-related accumulation of fat
270 mass and reduced insulin sensitivity that will also affect the parameters considered
271 here.[44,45] As indicated by our subgroup analyses in only pubertal children, metabolic
272 disturbances increase when entering puberty which suggests puberty to be a
273 sensitive time window for the development of MetS. Accordingly, Reinehr et al.[46]
274 showed that entering puberty doubled the risk of changing from metabolically healthy
275 obesity to metabolically unhealthy obesity in a cohort of obese children. However,
276 they further observed that this risk was reduced again in late puberty.

277 Finally, we found that hardly any children showing several MetS components became
278 metabolically healthy over time. This observation underlines the need for early
279 interventions which could be accomplished e.g. by use of the recently suggested
280 monitoring cut-offs for young children to detect MetS at pre-clinical stage.[6] A main
281 prevention priority in children should be to reduce obesity, as the starting point for
282 further metabolic disturbances.

283 The present study is not without limitations. Gustafson et al.[47] showed that both the
284 short-term and long-term diagnosis of the MetS based on cut-offs is quite unstable in
285 children due to influences of subject factors like time of day, concurrent (unknown)
286 illness, or prior energy/ macronutrient intake. We tried to mitigate this common
287 problem by application of very strict and highly standardized procedures as well as
288 by collection of fasting blood. For instance, for blood pressure adequate cuff sizes for
289 children were used and up to three repeated measurements were taken after a 5-
290 minute rest to ensure a high data quality. However, for identification of impaired
291 glucose tolerance, an oral glucose tolerance test would have been the preferred
292 method, which was not feasible in this large cohort. This means that there may be
293 more uncertainty in the classification of markers showing circadian variability. This
294 may be reflected by the wider confidence intervals that we obtained for these
295 markers. As we covered a broad age range of the children, the metabolic markers
296 may be further influenced by developmental stage and puberty. We dealt with this
297 problem in our subgroup analyses by age and puberty status but also by application
298 of recently published age-, sex- (and height-) specific cut-off values. The
299 IDEFICS/I.Family definition of the ‘monitoring’ and ‘action’ levels of the different
300 metabolic markers is the first one being based also on age- and sex-specific
301 reference values for blood markers.[6] However, as these reference values were
302 derived based on healthy IDEFICS/I.Family children, it is expected that there is

proportion of at least 10% and 5% of children falling above the monitoring and action levels, respectively, when applying the definition to a general subset of the IDEFICS/I.Family cohort as in the present study.

Our study also has several strengths, as it included a large, well phenotyped sample of European children that was examined based on a highly standardized protocol and quality control procedures. The main strength is the longitudinal nature including repeated blood collections over a six-year time span. Such data are particularly rare in children. This enabled us to investigate changes of the metabolic status over time. In addition, these complex survey data were analyzed with sophisticated statistical methods that helped to reduce the dimensionality of the data and to assess clustering and progression of metabolic risk factors over time. Assessment of determinants of metabolic health trajectories (like lifestyle, socioeconomic or genetic factors) was out of the scope of the present paper but will be a promising field for future research.

Conclusions

Abdominal obesity was found to be very persistent and may precede future metabolic disorders. In contrast, disturbances of lipid levels or hypertension as single metabolic risk factors seem to return to normality more easily. Thus, weight management and reducing obesity in order to prevent further metabolic disturbances should be a prevention priority in children.

Conflict of interest

All the authors declare that there are no conflicts of interest.

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Author statement

This manuscript represents original work that has not been published previously and is currently not considered by another journal. The authors confirm that the manuscript will not be published elsewhere in the same form, in English or in any other language, if it is accepted by the International Journal of Epidemiology.
Each author has seen and approved the contents of the submitted manuscript. All authors contributed to conception and design, acquisition of data, analysis or interpretation of data. Final approval of the version published was given by all the authors. All the authors revised the article critically for important intellectual content.

All references have been checked for accuracy and completeness by CB, a language check was performed by LL. CB will act as guarantor for the paper.

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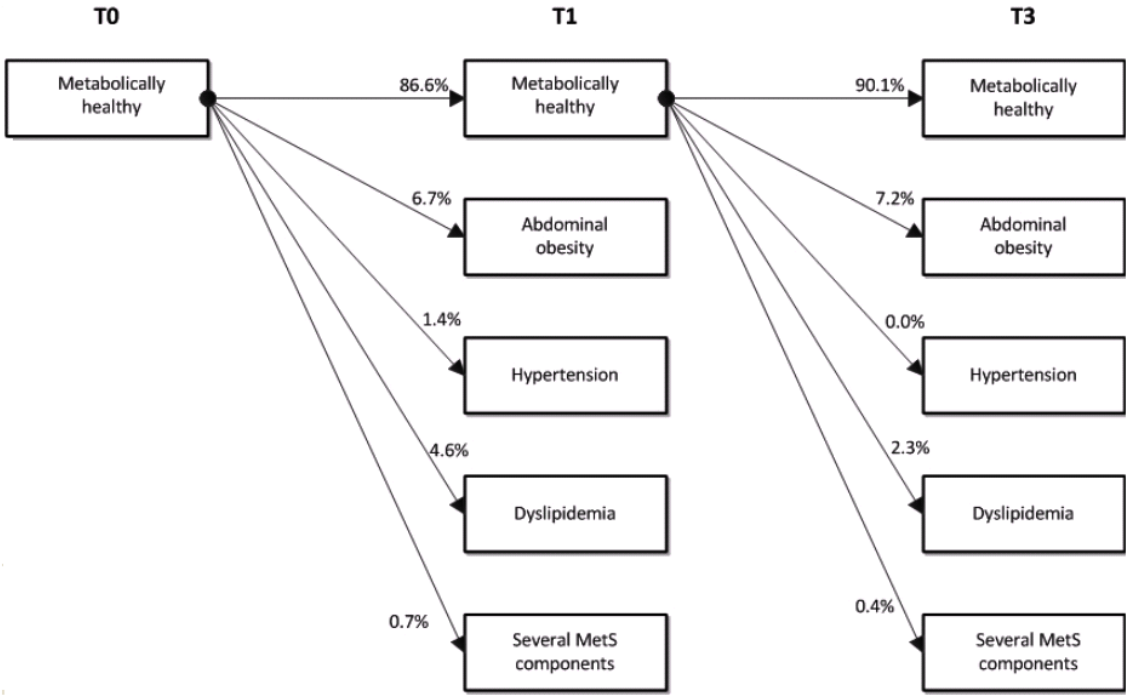
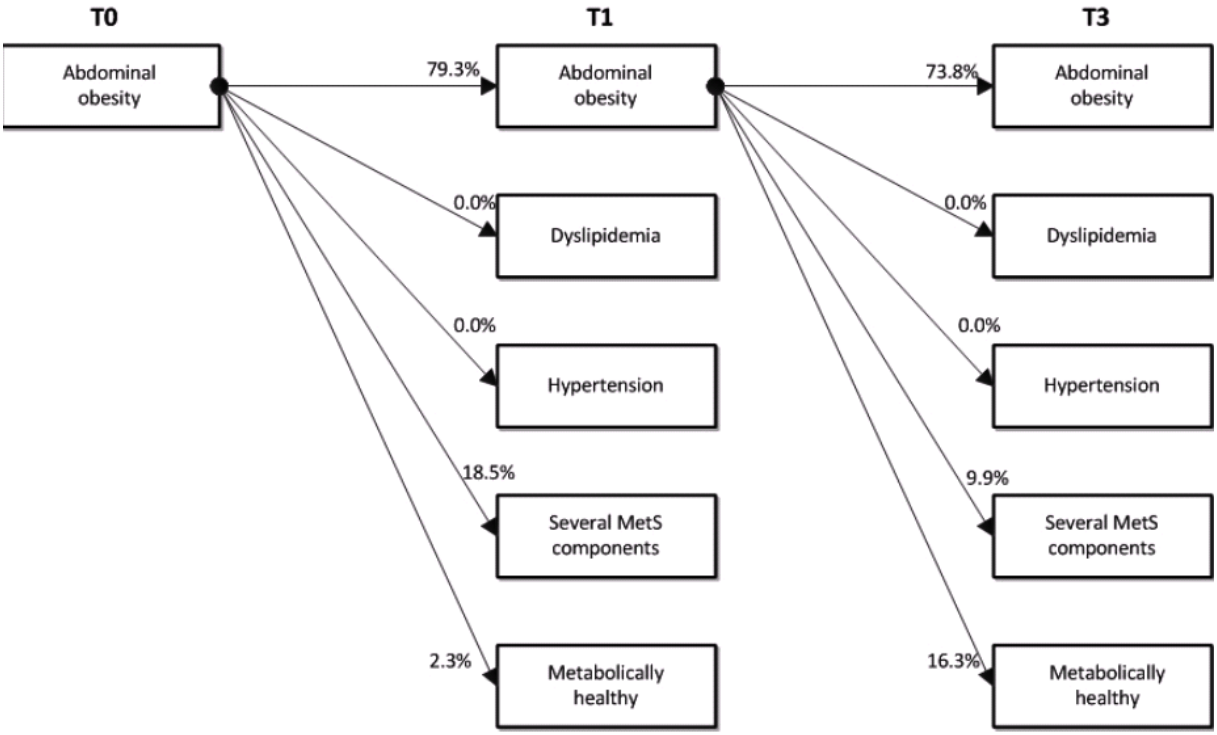

T0
T1
T3
Metabolically healthy
86.6%
Metabolically healthy
90.1%
Metabolically healthy
6.7%
Abdominal obesity
7.2%
Abdominal obesity
1.4%
Hypertension
0.0%
Hypertension
4.6%
Dyslipidemia
2.3%
Dyslipidemia
0.7%
Several MetS components
0.4%
Several MetS components


T0
T1
T3
Abdominal obesity
79.3%
Abdominal obesity
73.8%
Abdominal obesity
0.0%
Dyslipidemia
0.0%
Dyslipidemia
0.0%
Hypertension
0.0%
Hypertension
18.5%
Several MetS components
9.9%
Several MetS components
2.3%
Metabolically healthy
16.3%
Metabolically healthy

		T0			T1			T3		
		N	Mean	SD	N	Mean	SD	N	Mean	SD
Age [years]	Boys	3072	6.6	1.4	3227	8.3	1.6	2003	12.0	1.7
	Girls	3029	6.7	1.4	3222	8.4	1.6	1938	12.0	1.7
Waist circumference [cm]	Boys	3047	56.3	7.3	3216	60.5	9.0	1967	68.8	11.1
	Girls	3004	55.7	7.2	3212	59.6	8.7	1906	67.1	9.8
Systolic blood pressure [mmHg]	Boys	2990	101.9	9.3	3194	104.7	9.2	1954	107.9	9.9
	Girls	2949	101.4	9.3	3190	103.9	9.2	1886	106.7	9.4
Diastolic blood pressure [mmHg]	Boys	2990	63.0	6.6	3194	63.9	6.6	1954	63.7	6.5
	Girls	2949	63.9	6.6	3190	64.5	6.3	1886	64.8	6.5
Triglycerides [mg/dl]	Boys	2899	58.0	28.4	3102	58.5	27.8	1730	63.5	34.0
	Girls	2875	60.9	31.5	3111	62.2	27.5	1669	68.2	31.5
HDL-C [mg/dl]	Boys	2900	53.9	13.9	3127	54.6	13.6	1730	59.2	14.6
	Girls	2875	52.8	13.8	3135	52.3	13.5	1669	58.8	13.1
Glucose [mg/dl]	Boys	2900	86.4	9.5	3134	88.7	9.2	1711	94.8	7.1
	Girls	2875	83.9	9.1	3137	86.8	9.1	1658	93.1	6.7

Table 1: Means and standard deviations (SD) of age and cardio-metabolic parameters for the total study group and for the three examination waves T0, T1 and T3

Note: This table is based on a total of 6768 children providing each at least two repeated measurement of the different risk markers. The statistical model did not require children to have complete data in all three survey waves which is the reason for the varying numbers of observations with regard to the different markers.

	All						Males						Females					
	Normal level		> P90 and ≤ P95		> P95		Normal level		> P90 and ≤ P95		> P95		Normal level		> P90 and ≤ P95		> P95	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Waist T0	4475	74.0	339	5.6	1237	20.4	2248	73.8	166	5.5	634	20.8	2227	74.2	173	5.8	603	20.1
Waist T1	4443	69.1	424	6.6	1561	24.3	2224	69.1	180	5.6	813	25.3	2219	69.1	244	7.6	748	23.3
Waist T3	2631	67.9	247	6.4	995	25.7	1309	66.6	115	5.9	543	27.6	1322	69.4	132	6.9	452	23.7
BP T0	4795	80.7	530	8.9	614	10.3	2397	80.1	276	9.2	318	10.6	2398	81.3	254	8.6	296	10.0
BP T1	5141	80.5	573	9.0	670	10.5	2527	79.1	306	9.6	362	11.3	2614	82.0	267	8.4	308	9.7
BP T3	3219	83.8	320	8.3	301	7.8	1631	83.5	161	8.2	162	8.3	1588	84.2	159	8.4	139	7.4
Lipids T0	4792	83.0	473	8.2	508	8.8	2389	82.4	249	8.6	262	9.0	2403	83.6	224	7.8	246	8.6
Lipids T1	4990	80.6	622	10.0	583	9.4	2501	80.8	315	10.2	278	9.0	2489	80.3	307	9.9	305	9.8
Lipids T3	2791	82.1	297	8.7	311	9.2	1399	80.9	161	9.3	170	9.8	1392	83.4	136	8.2	141	8.5
Glucose T0	4844	83.9	449	7.8	482	8.4	2436	84.0	227	7.8	238	8.2	2408	83.8	222	7.7	244	8.5
Glucose T1	4876	77.9	592	9.5	790	12.6	2490	79.6	274	8.8	366	11.7	2386	76.3	318	10.2	424	13.6
Glucose T3	2612	77.5	341	10.1	416	12.4	1313	76.7	186	10.9	212	12.4	1299	78.4	155	9.4	204	12.3

Table 2: Children with normal levels, levels above monitoring but below action level (> P90 and ≤ P95) or above action level (> P95) at T0, T1 and T3 with respect to the four cardio-metabolic markers (total study group and stratified by sex; number of children and percentages)

BP: Blood pressure

P90, P95: age- and sex specific percentiles; for blood pressure also height-specific

Note: This table is based on a total of 6768 children providing each at least two repeated measurement of the different risk markers. The statistical model did not require children to have complete data in all three survey waves which is the reason for the varying numbers of observations with regard to the different markers and time points.

	Status 1: Metabolically healthy		Status 2: Abdominal obesity		Status 3: Hypertension		Status 4: Dyslipidemia		Status 5: Several MetS components	
	Prob	**95% CI**	**Prob**	**95% CI**	**Prob**	**95% CI**	**Prob**	**95% CI**	**Prob**	**95% CI**
Normal level: BP	91.5	(89.2;92.0)	82.3	(75.4;89.4)	17.8	(1.5;34.2)	85.4	(80.3;89.2)	55.2	(46.4;61.2)
Normal level: Waist	96.4	(94.9;97.9)	5.8	(2.1;12.3)	87.4	(77.2;92.4)	87.0	(77.9;91.0)	0.7	(0.0;2.9)
Normal level: Lipids	93.6	(91.5;96.7)	88.0	(84.1;92.3)	90.6	(86.2;94.1)	24.6	(0.6;48.5)	39.6	(19.8;51.7)
Normal level: Glucose	87.2	(86.2;88.2)	74.7	(70.6;78.8)	77.8	(72.8;82.1)	77.7	(72.6;81.7)	48.3	(41.6;54.6)
BP > P90 and ≤ P95	5.9	(5.1;7.0)	8.5	(5.9;10.8)	29.1	(23.3;35.1)	6.2	(4.1;8.7)	16.3	(13.5;19.4)
Waist > P90 and ≤ P95	2.9	(2.1;3.7)	19.3	(15.6;23.9)	6.5	(3.7;9.8)	7.1	(4.4;11.1)	2.0	(0.2;3.9)
Lipids > P90 and ≤ P95	4.1	(2.7;5.2)	7.8	(5.3;10.2)	5.8	(3.3;8.7)	33.3	(22.5;43.6)	23.7	(18.8;30.5)
Glucose > P90 and ≤ P95	6.7	(6.1;7.4)	13.0	(11.0;14.9)	11.2	(8.4;14.2)	9.5	(7.1;12.5)	13.9	(11.4;16.5)
BP > P95	2.6	(1.7;3.9)	9.3	(4.1;14.3)	53.1	(40.5;66.4)	8.4	(5.6;12.5)	28.5	(23.6;35.4)
Waist > P95	0.7	(0.0;1.5)	74.9	(65.8;81.4)	6.1	(2.9;17.3)	6.0	(3.0;12.8)	97.3	(94.5;99.4)
Lipids > P95	2.2	(0.4;3.5)	4.2	(2.0;6.4)	3.6	(1.6;6.2)	42.1	(30.0;57.0)	36.7	(28.3;51.3)
Glucose > P95	6.1	(5.4;6.8)	12.3	(9.1;15.5)	11.0	(8.2;14.7)	12.8	(9.9;16.5)	37.8	(31.4;44.4)

Table 3: Item-response probabilities in the identified latent groups, i.e. the numbers provide the probabilities of children having normal levels, being above the monitoring (P90) or being above the action level (P95) of the four metabolic markers, respectively, in the five latent groups reflecting children with distinct metabolic status. Item-response probabilities were constrained to be equal at all three time points

BP: Blood pressure
P90, P95: age- and sex specific percentiles; for blood pressure also height-specific
Prob: probability
95% CI: 95% confidence interval; bias-corrected bootstrap confidence intervals estimated using 5000 replicates (sample size: N=6768)

	Status 1: Metabolically healthy		Status 2: Abdominal obesity		Status 3: Hypertension		Status 4: Dyslipidemia		Status 5: Several MetS components	
	Prob	**95% CI**	**Prob**	**95% CI**	**Prob**	**95% CI**	**Prob**	**95% CI**	**Prob**	**95% CI**
T0	61.5	(60.5;62.4)	15.9	(15.2;16.7)	7.0	(6.5;7.5)	9.0	(8.6;9.5)	6.6	(6.1;7.0)
T1	56.5	(55.5;57.5)	17.2	(16.5;17.9)	7.3	(6.9;7.8)	8.4	(8.0;8.9)	10.5	(9.9;11.1)
T3	59.8	(58.8;60.7)	18.0	(17.4;18.7)	3.5	(3.2;3.8)	6.6	(6.2;6.9)	12.1	(11.5;12.7)

Prob: probability for group membership
95% CI: 95% confidence interval; confidence intervals calculated based on sample post probabilities

Table 4: Prevalence of latent statuses at T0 (mean age: 6.6y), T1 (mean age: 8.4y) and T3 (mean age: 12.0y) estimated based on latent transition analysis (probabilities for group memberships at T0, T1 and T3 and 95% confidence intervals)

Transition probabilities from T0 to T1 (95% CI in brackets)	**Status 1: Met. healthy T1**	**Status 2: Abdominal obesity T1**	**Status 3: Hypertension T1**	**Status 4: Dyslipidemia T1**	**Status 5: Several MetS comp. T1**
Status 1: Met. healthy T0	**86.6** (82.8;90.2)	6.7 (5.3;8.2)	1.4 (0.0;3.0)	4.6 (2.1;8.7)	0.7 (0.0;1.6)
Status 2: Abdominal obesity T0	2.3 (0.0;8.0)	**79.3** (69.8;86.1)	0.0 (0.0;0.7)	0.0 (0.0;2.8)	18.5 (12.0;26.1)
Status 3: Hypertension T0	0.6 (0.0;17.9)	0.4 (0.0;5.9)	**92.2** (85.3;99.4)	0.0 (0.0;9.9)	6.8 (2.7;13.2)
Status 4: Dyslipidemia T0	32.4 (10.4;50.3)	4.4 (0.0;9.9)	0.0 (0.0;6.7)	**62.1** (44.6;87.7)	1.2 (0.0;5.5)
Status 5: Several MetS comp. T0	0.0 (0.0;6.2)	0.0 (0.0;14.7)	0.0 (0.0;5.7)	0.2 (0.0;3.4)	**99.8** (96.4;100)
Transition probabilities from T1 to T3 (95% CI in brackets)	**Status 1: Met. healthy T3**	**Status 2: Abdominal obesity T3**	**Status 3: Hypertension T3**	**Status 4: Dyslipidemia T3**	**Status 5: Several MetS comp. T3**
Status 1: Met. healthy T1	**90.1** (86.8;93.7)	7.2 (5.4;9.7)	0.0 (0.0;2.8)	2.3 (0.0;5.9)	0.4 (0.0;1.6)
Status 2: Abdominal obesity T1	16.3 (11.6;22.8)	**73.8** (62.7;81.7)	0.0 (0.0;2.0)	0.0 (0.0;0.0)	9.9 (3.7;18.0)
Status 3: Hypertension T1	40.3 (27.2;51.1)	6.8 (0.0;16.5)	**47.2** (37.3;61.8)	0.0 (0.0;10.6)	5.7 (0.0;15.1)
Status 4: Dyslipidemia T1	35.1 (18.3;52.2)	0.0 (0.0;6.2)	0.6 (0.0;8.3)	**58.1** (42.7;77.5)	6.2 (1.1;14.0)
Status 5: Several MetS comp. T1	0.8 (0.0;5.0)	7.3 (0.0;17.0)	0.0 (0.0;1.7)	3.5 (0.2;8.9)	**88.3** (78.5;97.2)

Table 5: Transition probabilities (and 95% confidence intervals) from T0 to T1 as well as from T1 to T3, i.e. probabilities to change from a certain status at T0/T1 to another status at T1/T3 or to remain in the same status. Entries in bold font indicate membership in the same latent status at two consecutive time points.

95% CI: 95% confidence interval; bias-corrected bootstrap confidence intervals estimated using 5000 replicates (sample size: N=6768)

Supplementary material

Supplementary material S1: Detailed description of study measures

Anthropometric measurements

As part of the standardized anthropometric examination protocol, waist circumference [cm] was measured in upright position with relaxed abdomen and feet together, midway between the lowest rib margin and the iliac crest to the nearest 0.1 cm (inelastic tape: Seca 200; seca, Birmingham, UK).

Blood pressure

Blood pressure [mmHg] was measured with an automated oscillometric device (Welch Allyn 4200B-E2, Welch Allyn Inc. NY, USA) where the cuff length was chosen depending on the child's arm circumference. After at least 5 minutes of resting in a sitting position, two measurements were taken with two minutes interval in between, plus a third one in case the first and second measurements differed by >5%. The average of the two measurements showing the smallest difference was used in the subsequent analysis.

Collection of blood markers

Venous blood was collected in a fasting state from children and teens. At T0, fasting capillary blood was collected in case (parents of) young children refused venipuncture.

At T0 and T1, blood glucose, high-density lipoprotein-cholesterol (HDL-C) and triglycerides were assessed using a point-of-care analyser (Cholestech LDX, Cholestech Corp., Hayward, CA, USA). In T3, an enzymatic UV test (Cobas c701, Roche Diagnostics GmbH, Mannheim, Germany) was used for blood glucose, a homogeneous enzymatic colorimetric test (Cobas c701, Roche Diagnostics GmbH, Mannheim) for HDL-C and an enzymatic colorimetric test (Cobas c701, Roche Diagnostics GmbH, Mannheim, Germany) for triglycerides. Validation measurements were conducted confirming that the differing methods used yielded similar results. Blood samples were analyzed centrally in a laboratory accredited according to DIN EN ISO 15189 by the German Accreditation Council (in T3).

Supplementary material S2: Detailed description of statistical analyses

Applying the definition given in the section “Metabolic syndrome components”, variables were derived indicating children “with normal levels”, “above monitoring levels (P90)” and “above action levels (P95)” with respect to the four metabolic markers (waist circumference, blood pressure, lipid levels, blood glucose). These variables formed the basis to identify groups of children with similar metabolic status: LCA is a latent variable model that is used to identify underlying (unobserved) subgroups in a population [45]. Latent transition analysis (LTA) is a longitudinal extension of LCA that allows latent class membership to change over time; in this model, change is quantified by a matrix of transition probabilities between two consecutive time points [10]. LTA was used in the present analysis to identify groups of children with distinct metabolic status as well as transition probabilities over time (i.e. changes in the assignment to the different latent metabolic groups from T0 to T1 and from T1 to T3). LTA models can handle missing data assuming data to be missing at random such that all children (N=6768) with at least two measurements of the metabolic parameters over time were considered.

The four variables reflecting children’s classification according to the four components of the metabolic syndrome at T0, T1 and T3 were used to estimate probabilities (prevalence) for latent statuses at T0, T1 and T3, probabilities for transitions between latent statuses from T0 to T1 and T1 to T3 as well as item-response probabilities conditional on latent status membership (i.e. probabilities of showing normal levels or levels above the monitoring or action levels for the metabolic markers in the different latent statuses). The item-response probabilities were restricted to be equal across all times. This ensured to detect the same latent classes at T0, T1 and T3 which eases interpretability of model estimates and enhanced model fit.

Bootstrap was performed to estimate confidence intervals for the item-response and transition probabilities based on the original sample size of N=6768 with 5000 replicates using unrestricted random sampling. Starting values were estimated based on the initial sample. Bias-corrected (BC method) 95% confidence intervals were estimated to correct for skewness.

	T0		T1		T3	
	N	%	N	%	N	%
No component	2674	47.5	2607	42.5	1506	45.7
Wa	628	11.2	689	11.2	397	12.0
Lip	408	7.2	401	6.5	178	5.4
BP	466	8.3	467	7.6	189	5.7
Glu	349	6.2	457	7.4	240	7.3
Wa, Lip	164	2.9	227	3.7	123	3.7
Wa, BP	222	3.9	211	3.4	93	2.8
Glu, Wa	180	3.2	284	4.6	177	5.4
Glu, Lip	87	1.5	97	1.6	43	1.3
Glu, BP	82	1.5	108	1.8	48	1.5
BP, Lip	72	1.3	69	1.1	28	0.9
Wa, Lip, BP	81	1.4	95	1.6	40	1.2
Wa, Lip, Glu	71	1.3	174	2.8	100	3.0
WA, BP, Glu	86	1.5	123	2.0	57	1.7
Lip, BP, Glu	23	0.4	29	0.5	13	0.4
Wa, Lip, BP, Glu	40	0.7	101	1.7	67	2.0
Total sample size (N)	5633		6139		3299	

Supplementary material S3: Number of children and percentages showing no, one, two, three or all four components of the metabolic syndrome (i.e. waist circumference, lipids levels, blood pressure or blood glucose above monitoring level) at T0, T1 and T3

Wa: waist circumference above monitoring level

BP: blood pressure above monitoring level

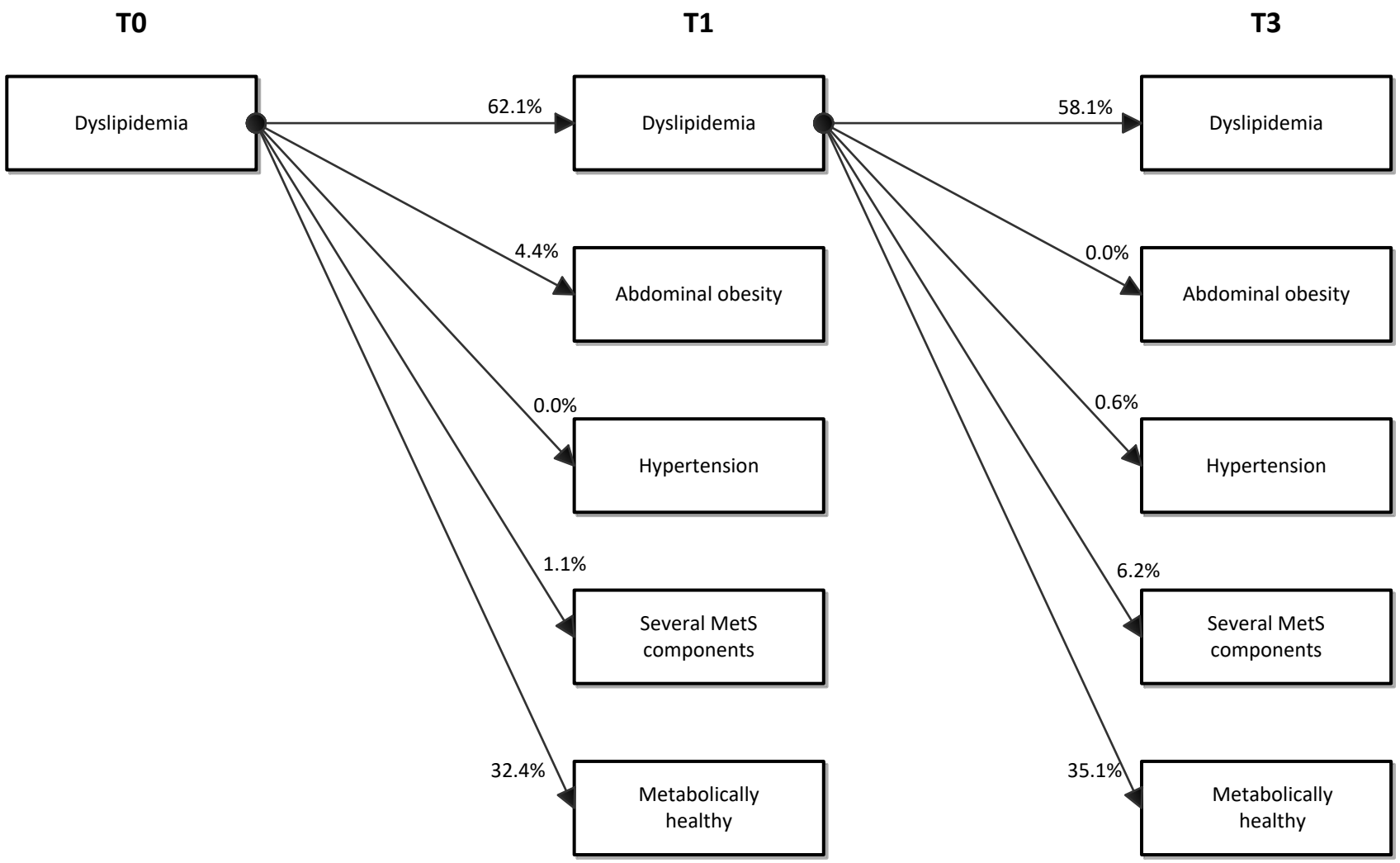
Lip: lipid levels above monitoring level

Glu: blood glucose above monitoring level

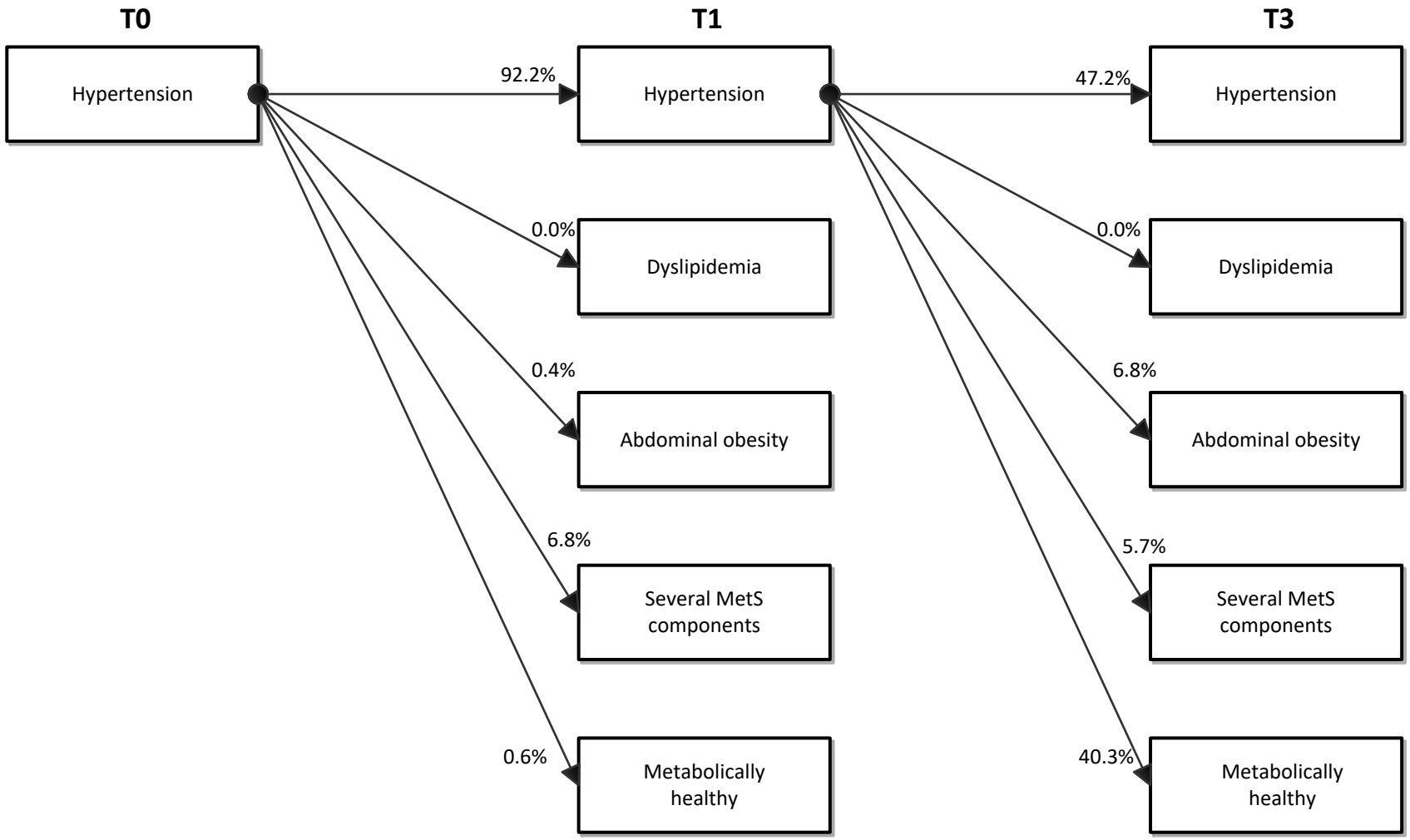
Covariates assessed at T0	Status 1: Metabolically healthy		Status 2: Abdominal obesity		Status 3: Hypertension		Status 4: Dyslipidemia		Status 5: Several MetS components	
	N	%	N	%	N	%	N	%	N	%
Boys	2084	49.5	542	50.9	183	51.8	247	54.5	197	50.6
Girls	2130	50.5	522	49.1	170	48.2	206	45.5	192	49.4
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age [years]	6.3	1.6	6.7	1.4	6.6	1.6	6.4	1.4	7.0	1.3
Body Mass Index	15.5	1.3	19.5	2.6	16.1	1.6	15.8	1.6	21.6	2.8
BMI z-score (Cole & Lobstein, 2012)	0.0	0.9	1.8	0.9	0.3	0.9	0.1	0.9	2.4	0.8

Table S4: Age, sex and BMI (z-score) distributions in the different metabolic statuses at T0

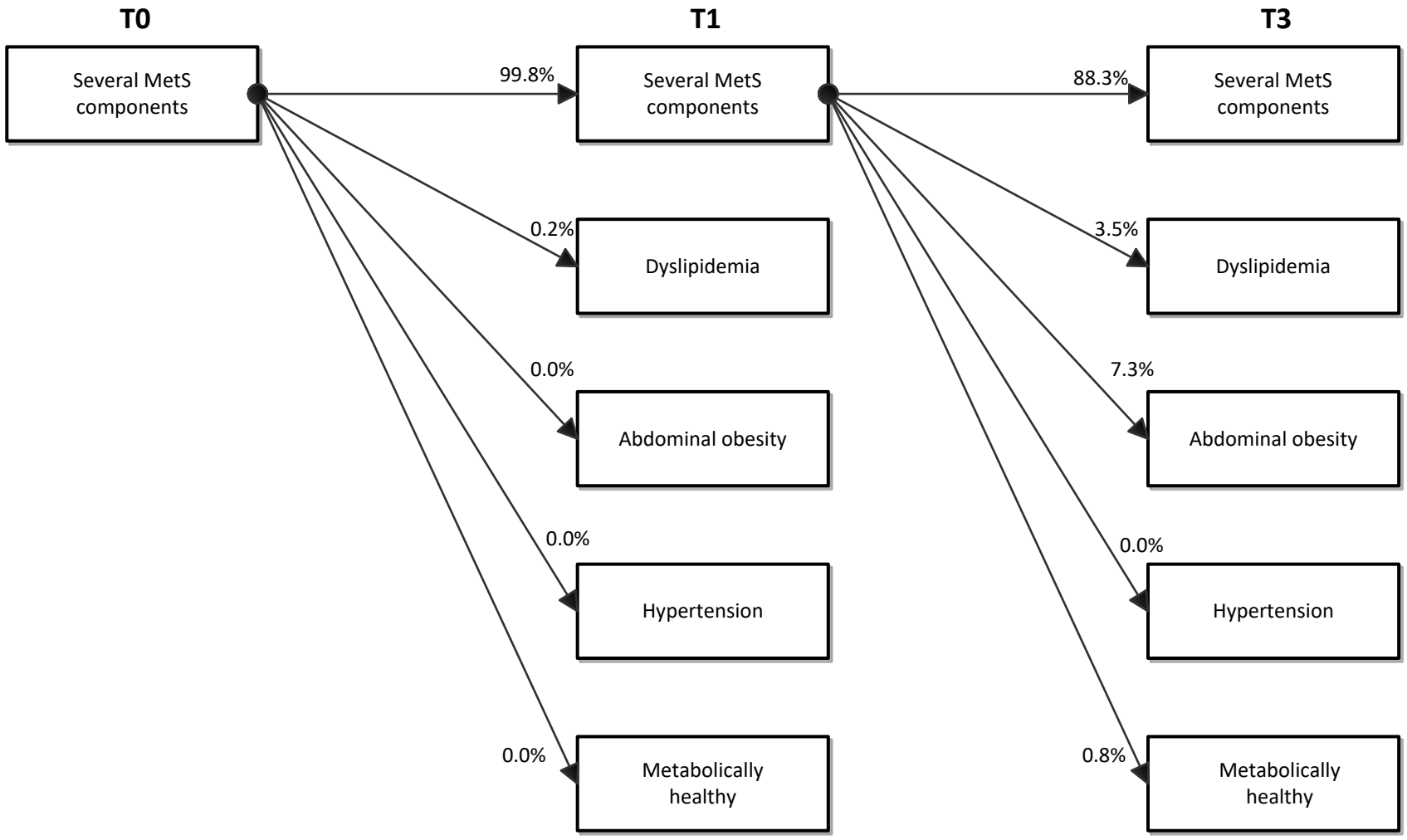
SD: standard deviation



Supplementary material S5: Transition probabilities from T0 to T1 as well as from T1 to T3 of children in the dyslipidemia group (9.0% at T0)



Supplementary material S6: Transition probabilities from T0 to T1 as well as from T1 to T3 of children in the hypertension group (7.0% at T0)



Supplementary material S7: Transition probabilities from T0 to T1 as well as from T1 to T3 of children in the group with several MetS components (6.6% at T0)

	Status 1: Metabolically healthy			Status 2: Abdominal obesity			Status 3: Hypertension			Status 4: Dyslipidemia			Status 5: Several MetS components		
	< 6y	**≥ 6y**	**Pub**	**< 6y**	**≥ 6y**	**Pub**	**< 6y**	**≥ 6y**	**Pub**	**< 6y**	**≥ 6y**	**Pub**	**< 6y**	**≥ 6y**	**Pub**
T0	67.5	57.7		12.1	18.0		6.9	8.7		10.2	7.3		3.2	8.3	
T1	64.1	52.2		15.5	17.8		7.6	8.4		7.2	7.7		5.5	13.9	
T3	62.0	58.3	53.4	20.6	17.1	21.0	3.1	5.8	7.3	4.2	6.5	4.1	10.1	12.3	14.2

Supplementary material S8: Prevalence of latent statuses at T0, T1 and T3 estimated using latent transition analysis separately for children aged < 6 years at baseline, children ≥ 6 years at baseline as well as for the subsample of children that entered puberty in T3 (N=1830; defined based on reported voice alterations in boys and start of menarche in girls)

Pub: subsample of children that already entered puberty in T3; pubertal status was only queried in T3

Supplementary material S9: Sensitivity analyses

Sensitivity analyses including only one child from each family to check whether our results are affected by the potential similarity among the 546 sibling pairs that were included in the study sample gave almost the same results.

In another two sensitivity analyses 1) only children participating at all three waves and providing information on all metabolic markers (N=1612; complete case analysis) and 2) all children providing at least one measurement for all metabolic markers (N=14582) were included. Again, results changed only marginally suggesting that we detected very stable patterns of metabolic status in this population.

In a subgroup analyses of children providing additional information on insulin (N=4013), HOMA-IR was calculated and used as marker for insulin resistance instead of fasting blood glucose. Results were again very similar leading to the decision to use the larger sample with available blood glucose measurement for the main analyses.

Between T0 and T1, an intervention for primary prevention of obesity was embedded in the IDEFICS study (see e.g. Ahrens et al. 2011, 2017). For this reason, all analyses were conducted stratified by control vs intervention group as well as excluding children not participating at T0 to preclude any intervention effects on our results. The percentage of children being allocated to the different latent statuses slightly differs between children from the control vs intervention regions (see Supplementary material S9). Children in the intervention region had a slightly higher probability of being in the abdominal obesity group at all time points (including T0) whereas children in the control region showed a slightly higher probability for several MetS components. However, the patterns of changing group memberships over time (transition probabilities) were quite identical such that the overall interpretation of results is not altered.

	Status 1: Metabolically healthy		Status 2: Abdominal obesity		Status 3: Hypertension		Status 4: Dyslipidemia		Status 5: Several MetS components	
	Prob	95% CI	Prob	95% CI	Prob	95% CI	Prob	95% CI	Prob	95% CI
Intervention region (N=3080)*										
T0	60.6	(59.1;62.1)	16.0	(14.9;17.1)	8.9	(8.1;9.7)	7.8	(7.1;8.5)	6.7	(6.0;7.4)
T1	54.6	(53.1;56.1)	18.9	(17.7;20.0)	8.7	(8.0;9.5)	6.6	(6.0;7.3)	11.2	(10.2;12.1)
T3	60.6	(59.3;62.0)	20.9	(19.9;21.9)	3.4	(3.0;3.8)	4.2	(3.8;4.7)	10.8	(9.9;11.6)
Control region (N=3021)*										
T0	59.1	(57.6;60.6)	14.9	(13.9;16.0)	6.9	(6.3;7.6)	9.6	(8.8;10.3)	9.4	(8.6;10.3)
T1	54.7	(53.2;56.2)	14.8	(13.8;15.8)	7.6	(6.9;8.3)	9.6	(8.9;10.4)	13.2	(12.2;14.3)
T3	54.9	(53.5;56.2)	14.9	(14.1;15.8)	6.4	(5.9;7.0)	9.2	(8.6;9.8)	14.5	(13.6;15.5)

Table S10: Prevalence of latent statuses at T0, T1 and T3 estimated based on latent transition analysis (probabilities for group memberships at T0, T1 and T3 and 95% confidence intervals) for the control and intervention regions

*Our study group of 6768 children consisted of 3080 (45.5%) children in the intervention region, 3021 (44.6%) children in the control region and 667 (9.9%) children being newly recruited at T1.