ABSTRACT

Aim: to investigate association between growth disorders in pre and post natal period and abnormal lipid profile in adolescents aged 12 -15 years old in Tanjungsari population.

Methods: a cohort study was conducted in 3350 children who were born in 1988-1990 in Tanjungsari Subdistrict, Sumedang, West Java. A complete anthropometric data since their birth were collected from October 2002 – February 2003. Inclusion criteria: Children who had birth weight in the range of ± 3 of standard deviation (SD). Post natal growth disorder based on Z score of height according to age group and height changes at the age of 0 – 12 months and 12 – 36 months. SGA criteria were determined based on cross tabulation between weight and birth length at birth. Study subjects were divided into control group, groups of pre natal, post natal and pre-postnatal growth disorder. All subjects were checked for lipid profiles. Statistical calculation used analysis of variance, t test and logistic regression.

312 subjects were included in this study, 73 were in control group, 90 subjects in postnatal, 96 subjects were in pre natal and 53 subjects were in pre-post natal growth disorder group.

Results: this study has not shown significant difference in risk factor of having abnormal lipid profile between normal control group and growth disorder group except for those in prenatal growth disorder group with RR = 2.375 (p=0.014).

Conclusion: the post natal growth disorder had not influenced lipid profile in adolescents with SGA. Recent BMI was an additional risk factor for pre-post natal growth disorder group.

Key words: abnormal lipid profile, SGA, post natal growth disorder, adolescent aged 12-15 years old, Z score.

INTRODUCTION

In some developed countries, prevalence of coronary heart disease (CHD) tends to decrease. On the other hand, in developing countries, CHD mortality rate is predicted to increase to 120% in women and 137% in men.1-4

Mortality cause by CHD in Indonesia tended to increase in the past two decades. In 1986 CHD mortality rate according to Survey Kesehatan Rumah Tangga was 9.7% and had become 26.3% in 2001. In West Java in 1999, cardiovascular disease had been the main cause of death in hospitalized patients.5-8

Studies on identifying new risk factors of CHD had been done lately. One of them is to study the influence of growth disorder during gestational period and after birth on CHD risk factors such as impaired glucose tolerance, non insulin dependent diabetes mellitus, hypertension, high LDL level, and metabolic syndrome.1,9-16 This study based on Barker’s hypothesis stated that chronic illness in adulthood had been programmed since prenatal life and this theory is well-known as fetal origins of adult disease.9-11

Intra uterine growth and development period is a critical period during human life time.17-18 Nutritional condition during pregnancy determines fetal growth. If the nutrition is inadequate, there will be fetal growth disorder and the baby will have low birth weight.1,12-14, 19-20

Several previous studies had showed that low birth weight
is associated with atherogenic lipid profile. Some studies were conducted in Netherlands, Croatia and Finland. Animal study showed diet manipulation during pregnancy had permanent effect on cholesterol synthesis and cholesterol level variation. Some epidemiological studies had shown association between pre and post natal growth period on plasma lipid profile in adolescent and adulthood. 

Epidemiologic research showed association between inadequate nutritional condition during pre natal period and early period after birth and atherogenic lipid profile and this would implicate health status in society. If Barker’s hypothesis has been proven, CHD prevention program is important to focus on improving nutritional status of pregnant women and early after birth period in childhood.

In Tanjungsari subdistrict, Sumedang, West Java since 14 years before we had collected data of 3,350 babies who were born between 1988 and 1990. We had evaluated regularly on their nutritional status since birth until they reached 12 years old. Data included gestational age, birth weight, birth length, head circumference, and anthropometric status at the age of 12 years old.

This study is aimed to investigate the association between growth disorders in pre and post natal period and abnormal lipid profile in adolescent aged 12 -15 years old in Tanjungsari population. Questions to be answered in this study are: a). Do children with growth disorder in pre and post natal period have more risks of having abnormal lipid profile when they reach age 12-15 years old compared to those whose growth is normal? b). Are lipid profiles of children who had growth disorder in post natal period better than those who had normal growth? c). Does their nutritional status have additional risk factor for abnormal lipid profile?

**METHODS**

This is a historical cohort study and conducted in conjunction with The Internal Medicine Department, study group on cerebrovascular disease, research unit Medical Faculty Padjajaran University/Dr. Hasan Sadikin hospital in Bandung and Frontier for Health Foundation. Field preparation activities was coordinated by Frontier for Health.

Study subjects were cohort population of growth study in Tanjungsari subdistrict who had complete data on birth weight, birth length, body weight and height until age of 36 months. Last menstrual period data in this were not valid, therefore they cannot be used to determine fullterm/small for gestational age (FT/AGA/SGA) based on cross tabulation birth weight and length according to intra uterine growth curve for body weight and birth length. Post natal growth disorder status was assessed based on Z-score of birth length according to age and Z-score birth length changes at the age of 0-12 months and 12-36 months. Study subjects are categorized in table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>SGA</th>
<th>Post natal Growth</th>
<th>Group categories (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>Good Good control (101)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>Good Bad Posnatal (267)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>Bad Bad Prenatal (128)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>Bad Good Pre-posnatal (68)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>Good Good</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>Good Good</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>Bad Bad</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>Bad Good</td>
<td></td>
</tr>
</tbody>
</table>

Subjects in group 1 were children who had birth weight and birth length fulfilling AGA criteria and had Z score of birth length according to age in range of ± 2 of standard of deviation (SD) and birth length changes at the age of 0-12 months and 12-36 months > 0.5 SD. Group 3 were children who had birth weight and birth length at birth fulfilling AGA criteria, had Z score of birth length according to age in range of < -2 of standard of deviation (SD) and birth length changes at the age of 0-12 months and 12-36 months < 0.5 SD. Group 5 were children having birth weight and birth length at birth fulfilling SGA criteria had Z score of birth length according to age in range of ± 2 of standard of deviation (SD) and birth length changes at the age of 0-12 months and 12-36 months > 0.5 SD. Group 7 were children who had birth weight and birth length at birth fulfilled SGA criteria and had Z score of birth length according to age in range of < -2 of standard of deviation (SD) and birth length changes of the age of 0-12 months and 12-36 months < 0.5 SD.

**Inclusion Criteria**

Study subjects whose birth weight and birth length at birth in accepted range of value in cohort population in Tanjungsari (± 3 Z score SD), had data on birth weight and birth length at the age of 0-36 months, 12-15 years old, and fulfilled the categories criteria of group 1, 3, 5, and 7.

**Exclusion Criteria**

Study subjects had moved outside Tanjungsari subdistrict.
Sampling
Study samples were obtained by stratified random sampling. First cohort population was stratified according to categories and simple random sampling was obtained from each category group. For group 1 and 7, we had done 100 % sampling and for groups 3 and 5 through simple random sampling.

Sample size
Sample size was determined based on study subjects included in the categorical definitions:

- Definitions of AGA and SGA were determined based on cross tabulation of birth weight and birth length according to intra uterine growth curve for weight and length at birth.\(^{55}\)
- Good post natal growth: if Z score of birth length according to age was in the range of ± 2 SD and body height at the of 1-12 months and 12-36 months > 0.5 SD.\(^{54-55}\)
- Bad post natal growth: if Z score of birth length according to age was in the range of ± -2 SD and body height at the of 1-12 months and 12-36 months < 0.5 SD.\(^{54-55}\)
- Cholesterol and triglyceride levels were examined using standard enzymatic reaction.
- Lipid profile: Abnormal lipid profile was assessed when there was one or more of these conditions were found; high total cholesterol, LDL or triglyceride level or low HDL level. Cut off value of high level of total cholesterol, LDL and triglyceride if > 95% percentile of normal distribution of cholesterol and triglyceride level in adolescent aged 12 – 15 years old. Low HDL level was considered when < 5% percentile.\(^{32}\)

Statistical Analysis
To observe the similar characteristics of independent variables between groups, descriptive data were described in percentage. Data in numeric scale were described in mean ± SD. ANOVA test was used to compare data in numeric scale. To answer questions no 1 and 3, we used logistic regression test. To answer question number 2 we used t test.\(^{56-57}\) All statistical calculation was done using soft ware SPSS 11.5 (SPSS, Inc, Chicago, Illinois). P value < 0.05 was considered statistically significant.

Limitation of Study
The limitations of this study are as follows: a). The study did not include other factors which could influence the result such as smoking habit, sex maturity rating, diet pattern and intake of study subjects; b). Number of study subjects in pre-post natal growth disorder was smaller than it should be; c). This study did not exclude primary congenital hyperlipidemia.

RESULTS
The study was conducted from October 2002 until Februari 2003. After validation of data, 2,618 adolescents fulfilled inclusion criteria and only 564 of them fulfilled the research categories. In this study only 312 study subjects were willing to participate in the study and consist of 159 females and 153 males. General characteristics of study subjects are shown in table 3.

Result in table 3 showed that adolescent with growth disorder in pre, post and pre-post natal period had mean body weight, height and BMI lower than those who had not growth disorder (control group). This result is in accordance to previous study that adolescent with growth disorder in pre natal and early post natal period at the age of 0-3 years old tended to have body weight and height lower than those whose growth was normal.\(^{10,11,17}\)

The data showed that group with only pre natal growth disorder had mean body weight, height and BMI higher than post and pre-post natal group. Pre-post natal group had the lowest body weight, height and BMI. This result indicated that post natal period was critical to adolescent growth and growth disorder at early post natal period would worsen growth disorder which had already occurred in pre natal period.
Li et al conducted a study on association between pre and post natal growth with body weight, height and body composition when they reach adulthood in 267 male and female subjects aged 21 – 27 years old. The result showed that pre and post natal growth disorder during second years of life associated with body weight and height in their adulthood. Both pre and post natal growth until 2 years of age had the same influence on body weight and height in adulthood.

**DISCUSSION**

**Lipid Profile of Adolescents Aged 12-15 Years Old with Pre, Post and Pre-post Natal Growth Disorder**

Lipid profile of adolescent aged 12-15 years old with growth disorder is shown in Table 4. This study indicated that adolescents aged 12-15 years old with pre, post and pre-post natal growth disorder had mean of total cholesterol, LDL and triglyceride level higher than those who did not have growth disorder (control group) although it was not statistically significant (p > 0.05), except for triglyceride with p = 0.04. Mean of HDL cholesterol in adolescents with growth disorder showed lower than control group but not statistically significant (p > 0.05). Figure 1 describes mean lipid level in adolescents aged 12-15 years old with and without growth disorder.

Table 4 and figure 1 shown above indicated that adolescents with pre-post natal growth disorder had the highest level of total cholesterol and LDL compared to control group and group with pre and post natal growth disorder although it was not statistically significant. This result is different from the previous study which indicated significant difference of cholesterol level

![Table 3. General Characteristics](image)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group n=73</th>
<th>Post natal group n=90</th>
<th>Pre natal group n=96</th>
<th>Pre-post natal group n=53</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>31 (43%)</td>
<td>45 (50%)</td>
<td>57 (59%)</td>
<td>26 (49%)</td>
<td>0.178</td>
</tr>
<tr>
<td>Male</td>
<td>42 (57%)</td>
<td>45 (50%)</td>
<td>39 (41%)</td>
<td>27 (51%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (years)</td>
<td>13.71</td>
<td>13.78</td>
<td>13.54</td>
<td>13.62</td>
<td>0.122</td>
</tr>
<tr>
<td>SD</td>
<td>0.75</td>
<td>0.67</td>
<td>0.68</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Body height</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (cm)</td>
<td>152.83</td>
<td>146.68</td>
<td>147.81</td>
<td>141.90</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>SD</td>
<td>7.84</td>
<td>7.98</td>
<td>6.75</td>
<td>8.20</td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (kg)</td>
<td>42.04</td>
<td>37.38</td>
<td>37.86</td>
<td>34.28</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>SD</td>
<td>7.94</td>
<td>7.26</td>
<td>7.41</td>
<td>6.48</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (kg/m²)</td>
<td>17.88</td>
<td>17.23</td>
<td>17.25</td>
<td>16.56</td>
<td>0.038 *</td>
</tr>
<tr>
<td>SD</td>
<td>2.38</td>
<td>2.03</td>
<td>2.65</td>
<td>3.05</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05 ; SD = standard deviation
The cause of the difference between this study and the previous one in the Netherlands is that study subjects of Netherlands were exposed to famine period once but economical improvement took place fast and subjects had more than adequate nutritional intake and tended to be fat. Nutritional status which was assessed from BMI level had mean 27.9 kg/m² in group exposed to undernourishment condition during the first trimester, 26.5 kg/m² in the second trimester and 26.7 kg/m² in third trimester. On the other hand, Tanjungsari was low socioeconomic status and this condition had not many changes when the babies had grown up to adolescent. Nutritional status represented by BMI in Tanjungsari actually were undernourished even for control group their BMI mean level was only 17.88 kg/m², while the normal BMI for adolescents was 18.5 – 24.99 kg/m².

**Association Between Pre, Post and Pre-post Natal Growth Disorder with Risk of Having Abnormal Plasma Lipid Level in Adolescents Aged 12-15 Years Old**

Logistic regression analysis was used to assess pre, post and pre-post natal growth disorder and risk of having abnormal plasma lipid level in adolescent aged 12-15 years old.

This study indicated that risk of having abnormal plasma lipid level in adolescent with growth disorder was not significantly difference from control group, except that pre natal group had higher risk to have higher triglyceride level with p = 0.014 and relative risk (RR) = 2.375. This result is in accordance with the previous study in US that children whose age 7-11 years old with history of low birth weight had triglyceride level higher than children with normal birth weight (p<0.05).

Other studies in the United States found association between low birth weight and low level of HDL cholesterol and high triglyceride level in children aged 4 – 14 years old.

Diet pattern in Indonesia which consists of high carbohydrate content may contribute to findings that show the relation between SGA and high triglyceride plasma level. Other conditions such as glucose intolerance and insulin resistance were also presumed to have relation with SGA, but this would need further studies to confirm.

Up to date, association between post natal growth disorder and plasma lipid level remains unclear. Previous study in Finland showed that post natal growth disorder (changes of body height from birth to age 5 years old < -2 SD) in children with SGA would have risk of having plasma total cholesterol 13.8 times higher (OR = 13.8; 95% CI 2.0-97.5). Other studies in Jamaica showed that plasma lipid level had inverse correlation with body height measured at time of study and was related with triceps skinfold thickness (p<0.001) in 6-16 years old.

Factors that may have influenced result of the study indicating no significant relation between growth disorder and risk of having high plasma cholesterol level in age of 12-15 years old were low social and economic condition, puberty period, genetics and diet pattern. Study in Jamaica showed that SGA in children with better socioeconomic conditions had higher total cholesterol than those who came from low social level. Result of this study might be different if subjects for control group were those with good nutritional status and normal BMI between 18.5-24.99 kg/m² not included in the cohort population.

Age population between 12 and 15 years old was puberty period and during this period the subjects had increased estrogen hormone level. This condition might contribute to study result because estrogen is known to have a role in lipid metabolism regulation and will increase LDL uptake, secretion and VLDL uptake by liver and will also increase synthesis of ApoA-1.

**Association Between Post Natal Growth Disorder in Group of Pre Natal Growth Disorder and Plasma Lipid Level in Adolescent Aged 12-15 Years Old**

This study showed that there was no significant difference of mean plasma level in group with SGA and early post natal growth disorder (0-3 years) compare to those in group with SGA but normal post natal growth. Association between post natal growth disorder and plasma lipid level in adolescent with SGA is shown in table 6.

This result is different from previous study in Finland which found adolescents with SGA would have higher risk as much as 13.8 times of having higher plasma total cholesterol if they had abnormal growth until age of...
Association of BMI at Time of Study with Risk of Having Abnormal Plasma Lipid Level in Adolescents in Age 12-15 Years Old with Pre, Post, Pre-post Natal Growth Disorder

Association between BMI at time of study with risk of having abnormal plasma lipid level in adolescents in aged 12-15 years old and pre, post, pre-post natal growth disorder was calculated using logistic regression analysis. The analysis is shown in table 7.

The result as shown above had indicated that BMI at time of study had not influenced plasma lipid level except for group with pre-post natal growth disorder. The BMI had changed p value of triglyceride level (p = 0.055) becoming statistically significant (p=0.048). This result is in accordance with the previous study in Finland that found that BMI at 12 years old had no influence on plasma cholesterol level. This result was also supported by another study in the Netherlands which found that atherogenic lipid profile in adulthood in group who were undernourished during prenatal period was not influenced by BMI in adulthood.25-26 This condition showed that pre-natal and early post natal growth had strong influence on lipid metabolism as in Lucas postulate.10,11

Table 5. Logistic Regression Analysis Between Pre Natal, Post Natal and Pre-Post Natal Growth Disorder and Plasma Lipid Level (Mg/Dl)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Cholesterol</th>
<th>LDL Cholesterol</th>
<th>HDL Cholesterol</th>
<th>Triglyceride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post natal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logistic coefficient (β)</td>
<td>-0,212</td>
<td>-0,919</td>
<td>-0,136</td>
<td>0,577</td>
</tr>
<tr>
<td>Exp β</td>
<td>0,809</td>
<td>0,399</td>
<td>0,873</td>
<td>1,781</td>
</tr>
<tr>
<td>P value</td>
<td>0,882</td>
<td>0,457</td>
<td>0,715</td>
<td>0,109</td>
</tr>
<tr>
<td>Prenatal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logistic coefficient (β)</td>
<td>0,437</td>
<td>-0,975</td>
<td>-0,143</td>
<td>0,865</td>
</tr>
<tr>
<td>Exp β</td>
<td>1,548</td>
<td>0,378</td>
<td>0,867</td>
<td>2,375</td>
</tr>
<tr>
<td>P value</td>
<td>0,723</td>
<td>0,430</td>
<td>0,698</td>
<td>0,014 *</td>
</tr>
<tr>
<td>Pre-posnatal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logistic coefficient (β)</td>
<td>1,463</td>
<td>-0,382</td>
<td>-0,470</td>
<td>0,770</td>
</tr>
<tr>
<td>Exp β</td>
<td>4,320</td>
<td>0,683</td>
<td>0,625</td>
<td>2,159</td>
</tr>
<tr>
<td>P value</td>
<td>0,211</td>
<td>0,758</td>
<td>0,302</td>
<td>0,055</td>
</tr>
</tbody>
</table>

*p < 0,05

5 years old compared to those whose growth was normal.26

The different result of this study from the study in Finland might be caused by different socioeconomic status between Tanjungsari and Finland. Nutritional status of study subjects in Finland represented by BMI in age 12 years old had mean BMI 19.8 kg/m2 in control group and 17.5 kg/m2 in SGA group, while in Tanjungsari both groups were undernourished with mean BMI in control group being 17.88 kg/m2 and groups with pre, post and pre-post natal growth disorder consecutively were 17.25 kg/m2, 17.23 kg/m2 and 16.56 kg/m2.

The influence of early post natal growth until age of 5 years old on cholesterol level remains unclear. Other study observing the influence of combination of pre and post natal growth disorder on CHD risk factor in adulthood was conducted by Baker et al in England. It showed that subjects with low birth weight gaining normal weight at age 1 year old had lower risk of CHD compared to those who were still underweight at age 1 year old. This condition might be caused by the resultant of several CHD risk factors. In that study, cholesterol level or other CHD risk factors were not observed.10,11

Table 6. Association Between Post Natal Growth Disorder in Group of Pre Natal Growth Disorder and Plasma Lipid Level in Adolescents Aged 12-15 Years Old

<table>
<thead>
<tr>
<th>Variable</th>
<th>t</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>-0,818</td>
<td>0,415</td>
<td>-11,704 – 4,854</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>-1,206</td>
<td>0,230</td>
<td>-11,771 – 2,849</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0,157</td>
<td>0,875</td>
<td>-3,371 – 3,953</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0,390</td>
<td>0,697</td>
<td>-14,275 – 2,289</td>
</tr>
</tbody>
</table>

95%CI = 95% Confidence Interval of the Difference

5 years old compared to those whose growth was normal.26

The different result of this study from the study in Finland might be caused by different socioeconomic status between Tanjungsari and Finland. Nutritional status of study subjects in Finland represented by BMI in age 12 years old had mean BMI 19.8 kg/m2 in control group and 17.5 kg/m2 in SGA group, while in Tanjungsari both groups were undernourished with mean BMI in control group being 17.88 kg/m2 and groups with pre, post and pre-post natal growth disorder consecutively were 17.25 kg/m2, 17.23 kg/m2 and 16.56 kg/m2.

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Association of BMI at Time of Study with Risk of Having Abnormal Plasma Lipid Level in Adolescents in Age 12-15 Years Old with Pre, Post, Pre-post Natal Growth Disorder

Association between BMI at time of study with risk of having abnormal plasma lipid level in adolescents in aged 12-15 years old and pre, post, pre-post natal growth disorder was calculated using logistic regression analysis. The analysis is shown in table 7.

The result as shown above had indicated that BMI at time of study had not influenced plasma lipid level except for group with pre-post natal growth disorder. The BMI had changed p value of triglyceride level (p = 0.055) becoming statistically significant (p=0.048). This result is in accordance with the previous study in Finland that found that BMI at 12 years old had no influence on plasma cholesterol level. This result was also supported by another study in the Netherlands which found that atherogenic lipid profile in adulthood in group who were undernourished during prenatal period was not influenced by BMI in adulthood.25-26 This condition showed that pre-natal and early post natal growth had strong influence on lipid metabolism as in Lucas postulate.10,11

The result of this study showed that risk of having abnormal plasma lipid level in adolescents with growth disorder had no significant difference compared to the normal control except for the pre natal growth disorder had high triglyceride level with p value = 0.014 and RR = 2.375.

CONCLUSION

Analysis on the influence of post natal growth disorder on lipid profile in pre natal growth disorder found no significant difference in mean level of plasma lipid
level in group with SGA who had early post natal growth disorder compared to those whose growth was normal. This study concludes that BMI is an additional risk factor in group with pre-post natal growth disorder.

REFERENCES


* previous p value > 0,05 (0,055) became < 0,05 (0,048)


