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RESEARCH ARTICLE

ANALYSIS OF THE DISTRIBUTION OF METABOLIC TYPES (META-TYPES) IN THE EUROPEAN POPULATION AND THEIR ASSOCIATION WITH DEMOGRAPHIC DATA

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ABSTRACT

Most weight loss programs focus on a low-carbohydrate diet. In terms of successful and sustainable weight loss however, this diet isn't suitable for every person as many studies demonstrate. One reason for this problem is the individual genetic make-up, since everyone metabolizes macronutrients differently. An individual diet plan for sustainable weight loss that is based on the genetic make-up and thus each person's metabolic subtype (Meta-type) is provided by the nutrigenetic analysis MetaCheck. The aim of this study was to investigate, if there is only one type of diet that is suitable for everyone, while considering the individual genetic predisposition. A statistical study with 16,641 randomly selected MetaCheck analysis results was carried out to analyze how the different Meta-types are distributed and whether there is any association between Meta-types and demographic data. The results demonstrate that different Meta-types are distributed quite evenly in the European population. Further the Meta-types are not associated with age, gender or BMI and demonstrate no person's risk for becoming overweight. In conclusion, general recommendations for everyone to lose weight isn't a promising solution. Instead, there is a strong need for an individualized weight loss therapy, which is based on the individual Meta-type.

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INTRODUCTION

Currently more than 2.1 billion people worldwide are overweight, which is defined as a body mass index (BMI) over 25 kg/m² (NCD Risk Factor Collaboration, 2016). Obesity, which is defined as a BMI of 30 kg/m² and more, affects around 671 million people worldwide and contributes to diabetes, hypertension, cardiovascular diseases, and especially cancer. From previous work, it was already known that obesity is strongly associated with 5 different cancer types (e. g. cancers of the colon, endometrium and kidney) (Vainio, 2002). A recent meta-analysis, which included more than 1,000 studies, identified eight additional cancer types linked to obesity, including postmenopausal breast cancer and ovarian cancer (Lauby-Secretan, 2016). Apart from an increased risk for different diseases, studies show that obesity also leads to a lower life expectancy and that a slightly elevated BMI already leads to a higher mortality. On the other hand, Ochner and colleagues point out that a weight reduction of only 5-10 % of the initial bodyweight can already decrease mortality and significantly improve the state of health (Ochner, 2015).

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However, even a modest long-term weight reduction is very difficult for most overweight and obese people. One part of the problem is that they are overloaded with a huge choice of different weight loss programs and nutritional advises. Today most popular weight loss programs are focused on a diet, which is very low in carbohydrates (low-carb diet). In terms of successful and sustainable weight loss, this type of diet is not suitable for every person in general as many studies clearly demonstrate (Shai, 2008 and Schwarzfuchs, 2012 and Johnston, 2014). Some are more successful than others. Along with this problem, lost bodyweight is often largely regained after the diet intervention has been terminated (Fothergill, 2016). Corresponding to this, Ochner and colleagues point out that a mere recommendation to avoid calorically dense foods might be no more effective for the typical weight losing patient than would be a recommendation to avoid sharp objects for someone bleeding profusely (Ochner, 2015). The universal dietary recommendations may have limited utility. A major cause for these differences in weight loss success is the genetic predisposition of every individual person as an increasing number of studies demonstrate. Based upon twin-, adoption-, and family studies as well as large population genetic studies, the heritability of body weight or the BMI is estimated at 40 – 70 % (Locke, 2015; Visscher, 2012). Different variants of metabolic genes can lead to great differences in the metabolism of macronutrients that are taken up with the food. Considering these facts, the Center of Genetic Analysis and Prognosis (CoGAP) in Germany developed the genetic metabolic analysis MetaCheck as described in (Askari, 2015 and Özüak, 2016). In the scope of this analysis, different gene variants are analyzed that are involved in the macronutrient metabolism and are demonstrably known to lead to a different food processing. As a result, CoGAP defines four different, metabolic subtypes the so called Meta-types (alpha, beta, gamma, and delta), which differ in their ability of processing carbohydrates, fats, and proteins. Meta-type alpha processes proteins well and should reduce the proportion of carbohydrate-rich and fat-containing food. The Meta-type beta processes proteins and fats well and should therefore focus on low-carb diet. Unlike alpha and beta, Meta-type gamma processes carbohydrates well, while Meta-type delta is good in processing carbohydrates and fats. In addition to each nutritional Meta-type one of two sport or exercise variants (endurance and speed) is defined for each person. The endurance variant is characterized by a high caloric consumption during endurance activities, while the speed variant shows a higher caloric consumption during speed-type based activities. With the determined Meta-type and sport variant, the best suitable diet and exercise form for a successful and sustainable weight loss can then be selected and an individual nutritional plan as well as sport plan can be created for each person. It is worth mentioning that the MetaCheck is not exclusively for overweight and obese people but also for everyone with normal weight that care for a healthy metabolism.

The different gene variants and the resulting Meta- and exercise-types suggest that there can't be just one type of diet, which leads to a successful and sustainable weight loss in every person. Nevertheless, most weight loss programs only recommend a combination of a low-carb diet and regular endurance sport, which would correspond to the combination Meta-type "Beta/E". The primary aim of this study is to investigate, if there is in fact only one type of diet that is suitable for everyone, while considering the individual genetic predisposition. For this purpose, a statistical study with 16,641 randomly selected MetaCheck analysis results was carried out to analyze how the different Meta- and exercise-types are distributed among the study participants and how big the differences are among the population regarding the genetic predisposition for macronutrient metabolism. Further, it was tested if the Meta-types and exercise-types are statistically and significantly associated with the demographic data (in this study: gender, age, and BMI) and the development of obesity.

Hypothesis Development

In scope of this work several hypotheses were developed and tested, to analyze different aspects and relationships of the four Meta-types and two exercise-types. The first hypothesis deals with the question, if there is a statistically significant association between the four different Meta-types and the two exercise-types. Likewise, two more hypotheses were made to analyze if there is a significant association between the Meta-types and different genders as well as between exercise-types and different genders. However, the main interesting hypotheses are, if any of the four Meta-types and two exercise-types are significantly associated with overweight and obesity (determined by the BMI), and therefore can be considered as a risk factor for developing overweight and obesity.

Considering the questions above, the following five hypotheses were developed:

A.) Meta-types and exercise-types

H0: There is no statistically significant association between Meta-types and exercise-types
H1: There is a statistically significant association between Meta-types and exercise-types

B.) Meta-types and gender

H0: There is no statistically significant association between Meta-types and gender
H1: There is a statistically significant association between Meta-types and gender

C.) Exercise-types and gender

H0: There is no statistically significant association between exercise-types and gender
H1: There is a statistically significant association between exercise-types and gender

D.) Meta-Types and BMI

H0: There is no statistically significant association between Meta-types and BMI
H1: There is a statistically significant association between Meta-types and BMI

E.) Exercise-types and BMI

H0: There is no statistically significant association between exercise-types and BMI
H1: There is a statistically significant association between exercise-types and BMI

MATERIALS AND METHODS

To determine the sample size with the highest possible statistical power a population size of 743,000,000 or more people, a confidence level of 99 %, and a confidence interval (also called margin of error) of 1 % were chosen and with the following sample size calculator equation calculated:

$$Sample\ Size = \frac{\frac{z^2 \times p(1-p)}{e^2}}{1+(\frac{z^2 \times p(1-p)}{e^2 N})}$$

(N = population size, e = margin of error, z = z-score)

The Meta- and exercise-type as well as the body mass index of all study participants were determined with the nutrigenetic MetaCheck analysis during 2012 and 2016. All necessary data for gender, age, height, and bodyweight were collected and analyzed in an anonymous manner. For the study, randomly selected participants were evaluated based on their BMIs as normal (18–24.9 kg/m^2), overweight (25 kg/m^2–29.9 kg/m^2), and obese (≥30 kg/m^2). For comparing the different sets of data, mean values and percentages of age, BMI, and bodyweight were calculated. Chi-square tests were used in intergroup comparisons of categorical variables. Categorical variables were expressed as numbers. P values lower than 0.01 were considered as statistically significant. The calculations were performed using the IBM SPSS Statistics V22 besides excel 2016.0. To assess if the four different Meta-types and the two different exercise-types are evenly distributed throughout the study samples, the total abundance of the four different Meta-types and two exercise-types as well as their percentages were used for statistical analysis. The Chi-Square Goodness-of-Fit Test was used to analyze if the distribution of the Meta- and exercise-types is homogenous. With a chi-square test of independence, it was analyzed if there is a significant association between the variables. The study was reviewed and approved by the ethics committee of the Fresenius University of Applied Sciences Köln, Germany.

RESULTS

As described in the method section, a sample size calculator equation was used, to determine the sample size with the highest possible statistical power for a population size of 743,000,000 or more people. The result was that a sample size of 16,641 MetaCheck-results are needed. Therefore, exactly 16,641 randomly selected samples were included in this study, to gain the highest possible statistical power. Of the 16,641 included participants 12,389 (74.4 %) were female and 4,252 (25.6 %) were male. Mean overall age was 43.6 (+/- 12.8) (Tab. 1). On average Women were 43.5 (+/-12.8) and men 44.0 (+/-12.6) years old. Mean overall bodyweight of all study participants was 81.4 (+/-18.6) kg. Women had a mean bodyweight of 77.0 (+/-17.0) kg; men 94.5 (+/-17.1) kg. Mean overall BMI was 28.0 (+/-5.7) kg/m^2. Women had a mean BMI of 27.6 (+/-5.9) kg/m^2, whereas men had a mean BMI of 29.0 (+/-4.9) kg/m^2. Tab. 2 shows the different amounts and percentages of the four different Meta-types, two exercise-types and combinations of Meta- and exercise-types. 4,969 (29.86 %) of 16,641 participants could be assigned to Meta-type Alpha, 3,929 (23.61%) to Meta-type Beta, 4,272 (25.67 %) to Meta-type Gamma, and 3,471 to Meta-type Delta (20.86 %). 10,410 (62.56 %) participants could be categorized as exercise-type E (Endurance). 6,231 (37.44 %) were assigned to exercise-type S (Speed). The Meta-type/exercise-type combination that shows the highest occurrence is G/E (19.97 %), whereas D/S is the combination that is represented in the lowest numbers (4.71 %). The results of the Chi-Square Goodness-of-Fit test showed highly significant differences regarding the abundance of the four Meta-types within the study population: X^2(3, N=16, 641)=287.27, p=0,00(α≤0.01). The difference in distribution of the two exercise-types is also highly significant: X^2(1, N=16,641) =1049.46, p=0,00 (α≤0.01). A chi-square test of independence was performed to examine a possible relation between the different Meta-types and exercise-types (Tab. 3). The relation between these variables was highly significant, X^2(3, N=16,641) = 1,402.77; p<.00001.

Table 1. Mean age, bodyweight, and BMI of study participants

	Mean x;¯	Standard deviation	Median
Age (years)	43.6	12.8	45
Women	43.5		
Men	44.0		
Bodyweight (kg)	81.4	18.6	79
Women	77.0		
Men	94.5		
BMI	28.0	5.7	26.9
Women	27.6		
Men	29.0		

Table 2. Distribution of Meta- and exercise-types

Meta-type	Percentages	Number
Alpha (A)	29.86 %	4,969
Beta (B)	23.61%	3,929
Gamma (G)	25.67 %	4,272
Delta (D)	20.86 %	3,471
Exercise type	Percentages	Number
Endurance (E)	62.56 %	10,410
Speed (S)	37.44 %	6,231
Meta- and exercise type	Percentages	Number
A/E	14.72 %	2,450
A/S	15.14 %	2,519
B/E	11.72 %	1,950
B/S	11.89 %	1,979
G/E	19.97 %	3,323
G/S	5.70 %	949
D/E	16.15 %	2,687
D/S	4.71 %	784

Table 3. Relation of Meta- and exercise-types

Results Chi-Square test - Meta-types and exercise-types			
	E (Endurance)	S (Speed)	*Row Totals*
Alpha	2,450 (3,108.42) (139.47)	2,519 (1,860.58) (233.00)	4,969
Beta	1,950 (2,457.84) (104.93)	1,979 (1,471.16) (175.30)	3,929
Gamma	3,323 (2,672.41) (158.39)	949 (1,599.59) (264.61)	4,272
Delta	2,687 (2,171.33) (122.47)	784 (1,299.67) (204.60)	3,471
Column Totals	10,410	6,231	16,641 (Grand Total)

The chi-square statistic is 1402.7712. The p-value is < 0.00001. The result is highly significant at p < .01.

The Meta-types Gamma and Delta show a significant difference between the distribution of exercise-types. A further chi-square test of independence was performed to examine the relation between the different Meta-types and gender (Tab. 4) as well as the two exercise-types and gender (Tab. 5). The relation between these variables was not statistically significant, X^2 (3,N=16,641)=3.32, p=0.344588 and X^2 (1,N=16641)= 0.0469, p=0.828595, respectively.

frequently recommended for the therapy of obesity. Furthermore, it was tested if there is a relation between the Meta- or exercise-types and gender, and if there is an association between Meta- or exercise types and BMI. Among the 16,641 study participants, 12,389 were women and 4,252 were men. The mean bodyweight for women was 77.0 (+/-17.0) kg with a mean BMI of 27.6 (+/-5.9) kg/m^2, while men had a mean bodyweight of 94.5 (+/-17.1) kg and a mean BMI

Table 4. Relation of Meta-types and gender

Results Chi-Square test - Exercise-types and gender			
	Women	Men	*Row Totals*
E (Endurance)	7,756 (7,750.10) (0.00)	2,654 (2,659.90) (0.01)	10,410
S (Speed)	4,633 (4,638.90) (0.01)	1,598 (1,592.10) (0.02)	6,231
Column Totals	12,389	4,252	16,641 (Grand Total)

The chi-square statistic is 0.0469.The p-value is 0.828595. The result is not significant, when p<0.01.

Table 5. Relation of exercise-types and gender

Results Chi-Square test - Meta-types and gender			
	Women	Men	*Row Totals*
Alpha	3,677 (3,699.35) (0.14)	1,292 (1,269.65) (0.39)	4,969
Beta	2,933 (2,925.09) (0.02)	996 (1,003.91) (0.06)	3,929
Gamma	3,219 (3,180.45) (0.47)	1,053 (1,091.55) (1.36)	4,272
Delta	2,560 (2,584.11) (0.22)	911 (886.89) (0.66)	3,471
Column Totals	12,389	4,252	16,641 (Grand Total)

The chi-square statistic is3.322. The p-value is 0.344588. The result is not significant, when p<0.01.

Table 6. Relation Meta-types and BMI

Resultat Chi-Quadrat-Test - BMI & Meta-types					
BMI	Alpha	Beta	Gamma	Delta	*Row Totals*
<18.5	21 (30.16) (2.78)	27 (23.85) (0.42)	25 (25.93) (0.03)	28 (21.07) (2.28)	101
18.5 - 24.9	1,710 (1,675.74) (0.70)	1,340 (1,325.01) (0.17)	1,428 (1,440.69) (0.11)	1,134 (1,170.56) (1.14)	5,612
25 – 29.9	1,707 (1,749.80) (1.05)	1,379 (1,383.57) (0.02)	1,522 (1,504.35) (0.21)	1,252 (1,222.29) (0.72)	5,860
≥30	1,531 (1,513.30) (0.21)	1,183 (1,196.57) (0.15)	1,297 (1,301.03) (0.01)	1,057 (1,057.09) (0.00)	5,068
Column Totals	4,969	3,929	4,272	3,471	16,641 (Grand Total)

The chi-square statistic is10.0012. The p-value is 0.350388. The result is not significant, when p<0.01.

Table 7. Relation exercise-types and BMI

			Results Chi-Quadrat-Test - BMI &Sport-types
BMI	E (Endurance)	S (Speed)	*Row Totals*
<18,5	62 (63.18) (0.02)	39 (37.82) (0.04)	101
18,5 - 24,9	3,503 (3,510.66) (0.02)	2,109 (2,101.34) (0.03)	5,612
25 – 29.9	3,645 (3,665.80) (0.12)	2,215 (2,194.20) (0.20)	5,860
≥30	3,200 (3,170.36) (0.28)	1,868 (1,897.64) (0.46)	5,068
Column Totals	10,410	6,231	16,641 (Grand Total)

The chi-square statistic is 1.1592.The p-value is 0.762795. The result is not significant, when p<0.01.

To evaluate if there is an association between the Meta- or exercise-types and BMI, a chi-square test of independence was performed. For both, Meta-types and exercise-types, no statistically significant differences in relation to BMI can be reported: X^2 (9, N=16,641)=10.00 (Tab. 6); p=0.35 and X^2 (3, N=16,641) = 1.16; p=0.76 (Tab. 7), respectively.

DISCUSSION & CONCLUSION

With more than 2.1 billion people being overweight or obese, obesity has become a critical global issue. Most popular weight loss programs focus today on a common low-carb diet, which is however not promising for everyone. The aim of this study was to analyze if the four metabolic subtypes and the two exercise-types that are defined by the genetic predisposition, are distributed evenly throughout the European population. Equally important was to evaluate with this research whether it is reasonable that a low carb diet and endurance sport are so

of 29.0 (+/-4.9) kg/m^2 (Tab. 1). It is not surprising that the men in our cohort are heavier and have a greater BMI, since men have a greater proportion of muscles and are on average larger in height. Nevertheless, women usually are more health-conscious then men and therefore tend to take steps for losing weight by doing the nutrigenetic test MetaCheck much earlier. This can explain the bodyweight and BMI differences among men and women in the cohort. Furthermore, the health awareness of women is the reason that more women do the MetaCheck than men. Our findings showed that even though in general more men are suffering from overweight than women (Mensink *et al*., 2013), there is no difference in distribution of the four Meta-types and the two exercise types among the two genders (Tab. 4 and 5). This clearly indicates that there is no association between a distinct Meta- or exercise-type and gender and therefore no Meta-type or exercise-type is more abundant among men or women. Another important question was, whether any of the four Meta-types and two exercise-types can be significantly associated with overweight and obesity and therefore be considered as a risk factor for developing overweight and obesity. The statistical analysis in this study shows that neither a distinct Meta-type nor one of the two exercise-types can be significantly associated with BMI (Tab. 6 und 7), thus, no Meta-type or exercise-type demonstrates a person's risk for becoming overweight. Interestingly, in this study a statistically highly significant relation between Meta-types and exercise-types can be reported. The Meta-types that metabolize carbohydrates well (Gamma and Delta), were connected to exercise-type "E" 3 to 3.5 times more often than to exercise-type S. This finding indicates the influence of evolutionary processes that led to the formation of different metabolic types. During the human evolution, the human genes had to adapt constantly to changing living conditions and environments. As hunter-gatherers, our ancestors consumed mainly meat which is rich in protein and fats. Carbohydrates only represented a small proportion of the consumed energy. Furthermore, hunter-gatherers needed to move quickly for hunting or escaping predators. When humans transitioned from hunter-gatherers to agricultural societies, the dietary habits as well as the physical demands changed. Now instead of speed, endurance was important for agricultural activities. Furthermore, with the growing of food crops, carbohydrates were increasingly included in the human diet. The results of this study indicate that the Meta-types Gamma and Delta are still strongly associated/connected with the exercise-type E. This kind of association could not be observed for the Meta-types Alpha and Beta, for which an evenly distribution of the exercise-types can be reported.

As mentioned in the introduction most popular weight loss programs today are focused on a low-carb diet and are often generally recommended in combination with endurance sports for overweight and obese people. With regard to the Meta Check this recommendation would correspond to the combination of Meta-type Beta and exercise-type E. Our study showed, however, that this specific combination only applied to 11.72 % of the population (Tab. 2). The finding that the four Meta-types are distributed evenly among the study participants suggests that it is not useful to give universal recommendations (e.g. low diet and endurance based sports) for everyone to lose weight effectively. Instead, an individual therapy for each person is necessary. This result is in line with a cohort study conducted by Zeevi *et al*. (2015), where the glycemic responses of 800 study participants were compared after the participants received identical meals. A high variability was found in the blood sugar curves and therefore in the metabolism of carbohydrates. Zeevi *et al*. conclude that universal dietary recommendations may have limited utility (Zeevi *et al*., 2015). The efficacy of individualized dietary and recommendations that consider the individual's unique genetic make-up were already proven in a retroperspective comparative study that was carried out at the Centre for Sport and Health Research (ZfG) of the German Sport University in 2013 (Kurscheid and Loewe, 2013). Patients that adjusted their nutrition and sports activities according to their MetaCheck results experienced a 5 times higher reduction in BMI compared to the control group that received general dietary recommendations. In line with this analysis, a retrospective study of the Stanford University published in March 2010 shows that a genetically adapted diet results in a greater weight loss success than a non-genotype based diet (Mindy Dopler Nelson *et al*., 2010). On average, the participants in the study who followed a genetically adapted diet successfully lost more than twice (about 2.5 times) as much weight than the comparison group with a non-genotype based diet. However, not all diets are successful in the long term, since lost bodyweight is often largely regained after quitting the diet intervention. Therefore, the sustainability of the weight loss success with MetaCheck was investigated in an empirical study, which was carried out in 2016 (Özüak *et al*., 2016). Nearly 91 % of the subjects reported that they could maintain their new weight, which underpins the sustainability of the weight reduction with MetaCheck.

To conclude, the results of this study demonstrate that different metabolic subtypes are indeed distributed quite evenly throughout the European study population and that there is not one major Meta-type. These findings as well as the findings of previous studies clearly indicate that a general recommendation for everyone to lose weightin a sustainable way is not an appropriate and promising solution. Instead, there is a strong need for anindividualized weight loss therapy which is based on the individual genetic make-upto avoid the often-described absence of weight loss success and weight regain. Overweight has already become a worldwide health problem and considering the individual genetic make-up via a nutrigenetic test like MetaCheck might be the solution for this worldwide growing problem.

Conflict of Interests

This study was financed by the Center of Genetic Analysis and Prognosis (Köln, Germany). R.C. Geibel was funded by the Fresenius University of Applied Sciences (Köln, Germany). A. van der Vegt, O. Özüak and H. Askari were funded by the Center of Genetic Analysis and Prognosis (Köln, Germany). Other additional financial or personal benefits regarding the study did not exist.

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