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Meta-analysis of genes in commercially available nutrigenomic tests denotes lack of association with dietary intake and nutrient-related pathologies

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Abstract

Nutrigenomics is an emerging discipline that aims to investigate how individual genetic composition correlates with dietary intake as well as how nutrition influences gene expression. Herein, the fundamental question relates to the value of nutrigenomics testing on the basis of the currently available scientific evidence. A thorough literature search has been conducted in PubMed scientific literature database for nutrigenomics research studies on 38 genes included in nutrigenomics tests provided by various private genetic testing laboratories. Data were subsequently meta-analysed to identify possible associations between the genes of interest and dietary intake and/or nutrient-related pathologies. Data analysis occurred according to four different models due to data sparsity and inconsistency. Data from 524,952 individuals (361,153 cases and 163,439 controls) in a total of 1,170 entries were obtained. Conflicting findings indicated that there was a great incompatibility regarding the associations (or their absence) identified. No specific - and statistically significant - association was identified for any of the 38 genes of interest. In those cases, where a weak association was demonstrated, evidence was based on a limited number of studies. As solid scientific evidence is currently lacking, commercially available nutrigenomics tests cannot be presently recommended. Notwithstanding, the need for a thorough and continuous nutrigenomics research is evident as it is a highly promising tool towards precision medicine.

Keywords: nutrigenomics, nutrigenomics testing, dietary intake, nutrition, genes, meta-analysis.

Introduction

Nutrigenomics is an emerging discipline that aims to investigate how individual genetic composition correlates with dietary intake as well as how nutrition influences gene expression (Affolter et al., 2009). To this end, nutrigenomics attempts to integrate the "omics" technologies (genomics, transcriptomics, epigenomics, metabolomics) in addition to post-translational modifications (Affolter et al., 2009; Liu and Qian, 2011). Personalized (genomic) medicine exploits genomic information in the context of guiding medical decision-making, thereby allowing physicians to make assessments of disease risk and design rational evidence-based treatment regimens. For this, the unique genomic profile of an individual has to be taken into consideration alongside their clinical profile to achieve a health-oriented decision (Pavlidis et al., 2012). However, being an emerging discipline, personalized medicine has yet to attain wide applicability in modern medical practice.

Nutrigenomic testing refers to the testing of genes that relate to conditions that are influenced by nutrition. To date, nutrigenomic testing is mostly provided using the direct-to-consumer (DTC) business model and given the fact that there is currently very limited information on its clinical validity, it is dealt with skepticism from the scientific community (Gulisano, 2013). This situation differs from pharmacogenomics and genetic testing of single gene disorders, where genotype-phenotype correlations are well established (Patrinos et al., 2013). To date, a large number of private genetic laboratories in several countries are providing nutrigenomic testing of several genomic variants that have been shown to be related with dietary intake and nutrition-related pathologies. Considering the fact that there are often contradictory findings as to whether these genomic variants can be correlated with such pathological inherited conditions, we sought to determine which

ones of these genomic variants can indeed be correlated with such inherited conditions and as such have a true prognostic nutrigenomic value.

Herein, a thorough literature search and meta-analysis of 38 genes analysed in commercially available nutrigenomic tests were conducted in an effort to highlight or overrule their prognostic value, questioning their use in nutrigenomic testing. In particular, we aimed to address whether: (a) these genes were indeed associated to various nutrition/food-related pathologies/diseases, (b) there were any solid clinical-evidenced guidelines on the use of the nutrigenomic tests available, (c) scientific results and indications validate the relationship between each gene or group of genes and the various nutrition/food-related diseases, and (d) the existing research literature could be used by healthcare professionals for diet/nutrition and medical testing and therapy purposes based on the results available to date.

Methods

A thorough search was conducted in the PubMed literature database for genotype-phenotype correlation studies on 38 genes using the following terms: “nutrigenomics”, “gene name” and “disease name” (Table 1). The 38 genes of interest were chosen following research on commercially available nutrigenomics tests and their specifics. Our meta-analysis included 1,170 entries published from 1995 to 2012. In total, 524,952 individuals (361,153 patients and 163,439 healthy individuals) from various ethnicities were considered. Related pathologies included obesity, diabetes, insulin resistance, hypertension, metabolic syndrome and gastrointestinal diseases (ulcerative colitis, crohn’s disease, HP, etc.). We focused on the genes of interest and their genomic variants (SNPs, indels, etc), the number of patients (cases) and controls, the date and type of study (single-

gene and genome-wide association study), the location and population details (e.g. gender, race/population, *etc*), groups' age, the phenotypic measures included, the allele and genotype frequencies as well as the overall outcome of each study. Diseases and conditions were grouped accordingly:

1. Cardiovascular Group (including ischemia and stroke)
2. Liver (hepatic) Group
3. Obesity Group
4. Metabolic syndrome, Diabetes and Insulin Resistance Group.
5. Lung and Respiratory Group
6. Cancer Group
7. Bone Disease Group
8. Lipid Group
9. Autoimmune Disease Group
10. Gastrointestinal Group
11. Anthropometry Group
12. Nephrology Group
13. Vascular Group
14. Neurology Group
15. Nutrient Group

16. Inflammation Group

17. Any other condition not included above

Data analysis occurred according to four different models due to data sparsity and inconsistency (Table 2).

Data mining and preprocessing

Data mining techniques were used to automatically obtain groups of SNPs or conditions that showed similar clustering according to the available association data. For all the genomic variants considered, the nature of their link with a condition was qualified by qualitative terms, such as: ‘yes’, ‘may’, ‘no’ and ‘unknown’ (Table 3). Then, the data derived from all studies and for every genomic variant were combined into a single record, called the ‘variant phenotypic profile’. Similarly, a ‘genotype profile’ was generated for each condition.

Initial examination of the phenotypic profiles revealed that they were very sparse since only a fraction of possible variant/condition associations had been reported in the literature. In addition to data sparsity, many inconsistencies between studies were observed. Since data sparsity and inconsistency are issues that cannot be ignored, they were taken into account in the design of the analysis methodology. Not only did we conduct an initial analysis attempting to identify similarities between phenotype and genotype profiles, but we also decided to reduce the impact of sparsity by performing further data exploration at a lower resolution. Although this might lead to a reduction of accuracy, manual inspection of novel patterns emerging from data mining should prevent any undesirable effect of the analysis protocol. First, we worked at the gene level: all

studies of SNPs related to a given gene were merged into a single profile, called the ‘gene phenotype’. Secondly, diseases and conditions were also grouped according to similarity for analysis purposes. A summary of the number of studies/results per model/analysis methodology is provided in Table 2.

Whatever the type of data, phenotypic and genotypic profiles were analysed to detect similarities between them. Note that we also investigated variants/genes displaying opposite effects. As in our previous work (Lanara et al., 2013), profile comparison and grouping were performed using a state-of-the-art data-mining tool, CLUTO (Rasmussen et al., 2003). More specifically, hierarchical agglomerative clustering was carried out to produce a binary tree representing similarities between profiles and highlighting possible groupings. Finally, the most informative groups were further analysed using the STRING 9.1 (http://string-db.org) database to collect additional evidence of associations.

A comprehensive list of supplemental references supporting the meta-analysis is presented under the supplemental materials section.

Results

Phenotypic Profiles

As anticipated, phenotypic profiles proved to be very sparse: despite 153 different genomic variants and 89 conditions were considered, only 679 different associations were revealed, i.e. 5% of the possible 13,617 associations. Since most associations have not been studied, our conclusions should be considered with extra caution. Moreover, a great number of inconsistencies were identified: in regards to the entire number of studies researched, 20% of the genomic variants displayed inconsistent phenotypic profiles,

whereas an additional 64% relied on results which have never been reproduced. Similarly, 33% of the conditions studied exhibited inconsistent results and 46% consisted of unreproduced associations. As expected, the aggregation of SNP profiles into 'gene phenotype' and grouping of diseases and conditions led to significant reductions of data sparsity from 95% to 88% and 68% 'unknown' associations, respectively, and an increase in data inconsistency (Table 4).

In the case of genomic variants with identical/similar phenotypes, our analysis revealed two *IL6* variants, namely rs1800797 and rs1800796. Identical/similar phenotypes for given conditions/diseases were also obtained for the *APOA1, APOA4, PON1, APOC3, MTHFR, APOA5* and *CRP* genes. This was not true for the phenotype profiles regarding *PON1* and *PON2* genes. At the gene level, new associations were obtained when the following comparisons were performed: *LIPC* vs *LDLR* vs *APOE*, *LDLR* vs *APOE*, *LDLR* vs *LIPC, LIPC* vs *APOE*, *UCP3-2* vs *UCP2, MTHFR* vs *MTR* vs *MTRR* and *LPL* vs *ADRB2*. Focusing on the resulting groups of conditions, only two similar conditions were obtained: (i) *HMGCR* (rs4704209, rs3761739, rs5909, rs3761738, rs17238540, rs10038095, rs3846663, rs2303152) was found to be related with the condition groups 4, 7 and 13 (metabolic syndrome, diabetes and insulin resistance group; bone disease group and vascular group respectively) and (ii) *LDL* (rs6413503) and *APOE* (rs440446) with groups 1, 9, 17 (Cardiovascular group, autoimmune disease group and other group respectively). When genes with similar phenotypes were investigated in regards to the condition groups, we have found that all clusters associations were quite weak (two out of the 17 groups). This was the case for the *APOA2* vs *ABCC6* vs *APOC4* vs *RXRA* vs *CUBN* genes and may be explained by the evidence of interaction between *APOA2, APOC4* and *RXRA*. It should be noted that the genes *FABP2* vs *CYP7B1* vs *MTP* and the *PPARA* vs *IL8* also showed some associations to specific groups.

Data inconsistency for all options/models of analysis

Herein, data inconsistency was profound. In brief, incompatible data were obtained for *IL6* (rs1800795 and rs1800796) as well as *ADRB3* genes (when searched at the gene level and the rs4994 level). Additionally, in the case of the *ADRB2* gene, 4 out of the 16 conditions were found incompatible, when we investigated *ADRB2* (rs1042714) in 26 studies, while 4 out of 10 incompatible conditions in 17 studies were found for *ADRB2* (rs1042713). Regarding the *CETP* gene, data showed 7 out of 18 incompatible conditions in the 113 studies studied. When the *CETP* was researched at the SNPs level (rs5882, rs708272, rs1800775), the outcome was similar. Notably, the *CRP* gene was found in 84 studies, among which 3 out of the 20 conditions studied were found to be incompatible. This is quite a low number, which needs to be further investigated and included in future metanalyses. At the SNPs level (rs1130864), only 1 condition in the 18 studies was found to be incompatible, while *CRP* (rs1205) has a high value and no incompatibility has been published, indicating straightforward single SNP associations. Additionally, the *APOA5* gene resulted in 3 out of 10 incompatible conditions in 47 studies and in 1 out of the 7 incompatible conditions in 11 studies, when the *APOA5* (rs2075291) was considered. Finally, two incompatible conditions were found in each one of the *APOC3*, *GSTP1*, *LIPC*, *LPL*, *PON1*, *TNF* and *UCP2*. Similar results were obtained when these conditions were investigated at the SNPs level. For the *MTHFR* gene, 1 out of the 14 conditions was found to be incompatible in 29 studies, which certainly requires further investigation. The SNPs of interest as well as their positive or negative association to the diseases/conditions studied is shown in Figure 1.

Non-incompatible results among the four options/models of research

Among the genes and their respective SNPs that we investigated in the various studies considered herein, there were many conditions, which were investigated devoid of incompatible results. However, due to the small amount of studies in some cases, we suggest that these points should be investigated further in a new meta-analysis by taking into account any new genome-wide association studies (GWAS) papers to include various and numerous populations. Notably, (i) *HMGCR*, *PPARA* and *IL8* genes (when all 3 were investigated at the gene level), (ii) *CRP* (when considered at the SNPs level), (iii) *MTRR* (gene and SNPs levels), (iv) *MTR* (gene and SNPs levels), (v) *TNF* SNPs level) and (vi) *IL6* genes (SNPs level) showed no incompatible results in a higher number of studies per condition (gene and/or SNPs level) ranging from 1.1 to 7 studies per condition.

Indeed, when looking at the datasets analysing the links of diseases/conditions to genes and/or SNPs, various points of interest were obtained. In the case of cardiovascular diseases/conditions we have found incompatibility among conditions and diseases such as coronary vasculopathy, hypertension, essential hypertension acute or not acute myocardial infraction, ischemic stroke and coronary heart disease. However, the incompatibility varied according to the number of total studies researched. As an example, in the case of coronary heart disease and hypertension, 1 gene out of the 2 researched was found incompatible in a total of 6 studies investigated, while in the case of essential hypertension incompatibility was found in 2 out of the 5 genes researched in the 25 studies regarding cardiovascular diseases that were investigated in our meta-analysis. In the case of gastrointestinal diseases and conditions, when 3 genes investigating celiac disease were studied in 10 studies, two of them were showed incompatible results. On the other hand, other gastrointestinal conditions such as crohn's disease, ulcerative colitis, helicobacter pylori, duodenal ulcer, esophageal cancer and its complications showed no incompatibility, however there was

only 1 study per condition. In the case of conditions/diseases such as weight/obesity/ lipid levels and various metabolic syndrome parameters (BMI, HDL-C, weight gain, triglycerides, visceral fat, abdominal adiposity, higher value of hip circumference, higher values of HDL-C, lower waist/hip ratio, metabolic syndrome, high plasma of cholesterol were researched), similar points were addressed except for the lack of incompatibility when the metabolic syndrome and the three genes researched were considered (among the 18 studies investigated). There was also a slight difference in regards to glucose and insulin conditions/diseases (glucose/insulin/diabetes/ insulin resistance/plasma insulin levels/elevated glucose levels/ gestational diabetes mellitus and carbohydrate metabolism), where studies per gene/SNP were ranging from 1 to 2.8. Finally, cervical cancer seems to be an emerging important result, although this is a non-nutrigenomic condition. Instead, its evaluation was encouraged, as it was investigated in many of the studies described herein. Indeed, the link to cervical cancer was investigated in two genes in 13 studies, leading to 6.5 studies per gene. This outcome should be further investigated in a meta-analysis of cancer genes. Lastly, regarding the link to SLE, there were only 1 to 1.4 studies per SNP/gene, indicating that further research is also needed.

The outcome on the diseases/conditions studied and the resulted associations with obesity, weight gain, insulin sensitivity-resistanse, diabetes and glucose levels

Regarding obesity, only 1 study showed a positive result when the association of the *ADRA2B* gene and obesity was investigated, being however population-specific. No links were found to weight gain, while the rest of the studies focused on traits, such as CVD, hypertension, insulin secretion, type 2 diabetes, heart rate, physical activity, diet and incident diabetes, anthropometric and metabolic phenotypes, essential hypertension with or

without type 2 diabetes mellitus, metabolic syndrome, sudden cardiac death and silent myocardial ischemia. In terms of the *ADRB3* gene and obesity only conflicting results were obtained, whereas only one study showing no link to obesity was obtained for *CRP*. Regarding diabetes, five studies showed positive and negative links to the disease among which one study revealed conflicting results. No link was found in the only study researching *IRS -1* and type 2 diabetes. In the case of the IL6 gene and diabetes, it seems that a positive link exists, however this refers to only three studies. In addition, only one study showed a positive association between *PON1* and diabetes and *ApoA1* and diabetes, whereas a negative association was revealed, when *ABCA1* was studied. A study for the *GSTT1* and *GSTM1* investigating their link to type 1 diabetes showed no association. Data on *LPL* and *UCP3* imply a link to insulin sensitivity. Another study investigated the possible association between insulin resistance and *APOA5* and showed no association. On the other hand, one study showed a 'small yes' association between LPL and insulin resistance and two studies a 'may' association between *UCP2* and *UCP2-3*, while another study showed a positive association between *ADRB1* and diabetes type 2. No association was found between *ADRA2A* and diabetes in one study, whereas a positive association was obtained between *ADRA2B* and diabetes type 2. Finally, only one study showed no association between the fasting glucose levels of *ADRA2A* and glucose levels. Notably, there were conflicting results for the *CRP* gene and negative association data for *IL1a* and *IL6*. Conflicting results were also obtained for *SLC30A8* and *TLCFL2*.

Gastrointestinal conditions/diseases

Regarding the gastrointestinal conditions and diseases, one study showed conflicting results on *TNF* and ulcerative colitis as well as a negative link between the

latter and *HLA*. The *IL10* showed negative results, while for the *IL1* gene conflicting results were shown for *Helicobacter pylori*. In the case of the *TNF* gene, there were more negative results for *Helicobacter pylori* and only one study showing positive results for the *-308AG* genotype. No link to gastric ulcer was found among the studies considered.

STRING software analysis

When the relationships between *ADRB1-ADRB3* and *ADRA1A-ADRA1B* were investigated, a strong association was obtained. Similar findings were obtained for *SOD2* and *SOD3*. These results were not found in our meta-analysis. In brief, the conflicting results are shown in Supplementary Figures 1-5. Additionally, the absence of statistical association between genes/SNPs and condition/diseases group is depicted in Supplementary Figure 6. Data incompatibility is summarised in Tables 3 and 4. Finally, a representation of the number of studies per genes researched for certain diseases and conditions are found in Supplementary Figures 7-21.

Discussion

The need to investigate the field of nutrigenomics via a meta-analysis approach arose since our group started noticing that extensive literature was published throughout the years regarding nutrigenomics analysis, nutrigenomics tests and gene/ variations interactions with diseases influenced by nutrition. However, research studies were so far discontinuous and thus, not many final conclusions were made for diseases/conditions and/or nutrients of interest. There were sparse results and various single referenced studies,

assuming that certain genes/mutations were associated or not to certain diseases and conditions emerged. Finally, the lack of regulation shows that there are no specific recommendations and guidelines till now in order to apply these tests in everyday life. It seems also that health professionals, but also in some cases the general public, are not totally ready for the use of these tests or they cannot fully understand or interpret them (Pavlidis et al., 2012). The need for an enhanced education/training on this field as well as data interpretation became evident in our previous study on nutrigenomics perceptions and views in Greece (Pavlidis et al., 2012). On the other hand, extra care should be given when these tests are prescribed, as their use is not yet well defined by law and by the scientific community through clinical research.

The trend of DTC and nutrigenomics testing is becoming more known to our society. Patrinos and co-workers (2013) discussed the various categories of genetic testing, one of which includes genetic tests designed to diagnose complex health conditions (Patrinos et al., 2013). In these tests, as described, where a risk for obtaining false-positive or false negative results is high, misinterpretation could often occur. Extra care should be given as misinterpretation could lead to an increased cost of the diagnostic procedures used, which were not probably needed or have the opposite effect (Patrinos et al., 2013). In the latter case, the individual becomes less vigilant about their health. At this point, we should not forget that there are very few qualified healthcare professionals to interpret the nutrigenomics tests results to individuals from the general population. As a consequence, results may not be well perceived, understood and even be acted on. Nevertheless, there is a tendency in believing that personalised nutrition would be more helpful (Pavlidis et al., 2012; Hurliman et al., 2014).

Direct to consumer testing is defined as the sale and use of genetic testing that does not include the involvement of the health care provider (Goddard et al., 2008). Companies

offering such tests via the Internet, pharmacies and in any other commercial way are spread worldwide and grow rapidly. An increase of DTC genetic tests from 14 to 84 instances (or 53 unique tests) was shown from a study in 2008 (Thompson et al., 2011) in only four years. Among those tests, nutrigenomics testing was also largely included.

The findings of our analysis are limited, however, there are important points highlighted which may benefit from futher investigation, when new research arises with more GWAS studies included. There were very few associations and in some cases, they were based on a few studies, such as one or two studies per gene or snp or condition. In some limited cases, we have found associations that were not expected, whereas in many cases there were conflicting results. When looking at the literature for the genes usually found in nutrigenomics testing and via various companies offering DTC genetic tests on nutrigenomics, we have noticed that, generally, no clear association was supported by the existing scientific evidence. Indeed, we have grouped the genes involved in the nutrigenomics tests analysed mainly according to diseases and conditions and not to the effect of the nutrients to a specific disease or condition (we have found very few studies on these points), as we have not found many studies on these associations. For instance, it is widely known that ω-fatty acids help against the risk factors of CVD, however, we have not found many studies that investigated the role of these fatty acids according to the genomic variants carried by the individuals. It should be noted that the field of nutrigenomics is highly complex, as it relies on nutrients, conditions and diseases, medical history and also eating habits, as well as genes. Our study, to our knowledge, is one of the very few to investigate and apply a meta-analysis for thirty-eight genes usually involved in nutrigenomics from a of diseases point of view that are mainly influenced by nutrition. Today, there is a lot more to be investigated and this study sets the pace for further research on all genes involved in nutrigenomics with more GWAS studies, as these will be

more useful by including more individuals. We have found a limited amount of GWAS through our literature search and of course, this is a starting point for the future investigation of genes involved in nutrigenomics that will help the future of designing personalised nutrition, personalised diets as well as personalised medical nutritional therapy through the effect of the nutrients, the genes and the SNPs involved. Diseases/pathologies such as obesity, diabetes, cardiovascular conditions, metabolic syndrome, gastrointestinal conditions as well as factors (weight, BMI), but also lipid levels, cholesterol and triglyceride levels, would all possibly be aided by the use of nutrigenomics, when further research is available. The research and scientific community supports that in the field of nutrigenomics more should be done in the models of applying this science for personalised nutrition (Gulisano, 2013; Ordovás Muñoz, 2013). Different types of diets, using various methods, such as the blood type and diet combination are not supported by research (Wang et al., 2014). It is true that another study focusing on the *PPAR, ADRB2, ADRB3, IL6, LIPC, LEP, LEPR* and *UCP3* genes led to variable results, when looked at their association to obesity and the outcome of fat restricted diet (Martinez et al., 2008). Additionally, one review showed a metabolic response to omega3 fatty acid supplementation for the APOE genotype and age/gender/BMI (Thifault et al., 2013). All these results in a whole show that there is a lot yet to be researched and the field of personalised diet and nutrition is ready for more studies designed in large mixed populations in order to include all possible genetic variations and polymorphisms.

The fact that nutrigenomics is a wide field that involves genes/mutations/conditions/diseases/food/nutrients etc, does not allow in such a preliminary state to proceed to the use of nutrigenomics testing in the general public. This is also stated by the position of the American Academy of Nutrition and Dietetics in 2014 (Camp and Trujilo, 2014), which identifies the problems in applying in such an early state

without specific research on nutrigenomics, the use of nutrigenomics testing for the treatment of diseases/conditions. In fact, this position states that mutations are only partially predictive of disease risk and shows the lack of education of the dietitians to interpret such results. Many years would be probably needed in order to have definite results clinically and scientifically proven, which will then be applied to our everyday life and the future era of personalised medicine and nutrition. It would be a great scientific progress in the clinical field if we could treat patients according to their genes, mutations and have hands-on experience of how nutrient and diet interacts with them and the person itself.

Conclusions

The present study, involving meta-analysis of over half a million cases, indicated that there are conflicting findings and a great incompatibility as far as associations between genomic variants with nutrient-relate pathologies and dietary intake are considered. In the vast majority of cases, there was no statistically significant association for any of the 38 genes of interest, whereas even in the very few cases where a weak association was found, this was based on a very limited number of studies. We feel that nutrigenomic testing should not be yet provided as a commercial service by genetic laboratories, as solid scientific evidence is currently lacking for the genomic basis of nutrient-related pathologies and phenotypes. Notwithstanding, continuous research will allow patients' treatment according to their genomic variants and their interactions with nutrients and diet. In this context, metabolomics and in particular, nutri-metabolomics data as well as multi-

omics data integration are anticipated to play a key role (Mounayar et al., 2014; Montague et al., 2014).

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List of Abbreviations

- AA: advanced atherosclerosis
- AASK: African-American Study of Kidney Disease and Hypertension
- ACS: Acute Coronary Ischemia
- ACS: acute coronary syndrome (s)
- AMI: acute myocardial infarction
- BC: breast cancer
- BMD: bone mineral density
- BRCA: breast cancer risk
- CAC: carotid artery compliance
- CAGB: coronary artery bypass graft
- CAD: coronary artery disease
- CD: celiac disease
- CHD: coronary heart disease
- CHF: chronic heart failure
- CIMT: carotid intima media thickness
- CKD: chronic kidney disease
- COPD: chronic obstructive pulmonary disease
- CRC: colorectal cancer
- CRC: Colorectal Cancer
- CRI: chronic renal insufficiency
- CV: coronary vasculopathy
- CVD: cardiovascular disease
- DN: diabetic nephropathy
- DPN: diabetic polyneuropathy
- EH: essential hypertension
- ESRD: end-stage renal disease
- FCH: familial combined hypercholesterolemia
- FH: familial hypercholesterolemia
- FMD: brachial artery flow-mediated vasodilatation
- GC: gastric cancer
- GH : gestational hypertension,
- GPL: gastric pre-cancerous lesions
- HALP: Hyperalphalipoproteinemia
- HCC: hepatocellular carcinoma
- HRV: Heart rate variability
- IBD: inflammatory bowel disease
- IHD: ischemic heart disease
- IMT : carotid intima-media thickness
- IPF: Idiopathic Pulmonary Fibrosis
- IS: ischemic stroke
- MI: myocardial infraction
- MS: metabolic syndrome

- NAFLD: Non-alcoholic fatty liver disease
- NASH: non-alcoholic steatohepatitis
- OA: osteoarthritis
- PAD: peripheral arterial disease
- PD: Parkinson’s disease
- PDB : Paget’s disease of bone
- PDR: proliferative diabetic retinopathy
- PE: preeclampsia
- PSA: psoriasis
- RA: rheumatoid arthritis
- RA: rheumatoid arthritis
- RCR: renal cancer risk
- tHcy : plasma homocysteine
- VAHC: Veterans Affairs Hypertension Cohort
- VTE: venus thromboembolism
- UC: ulcerative colitis

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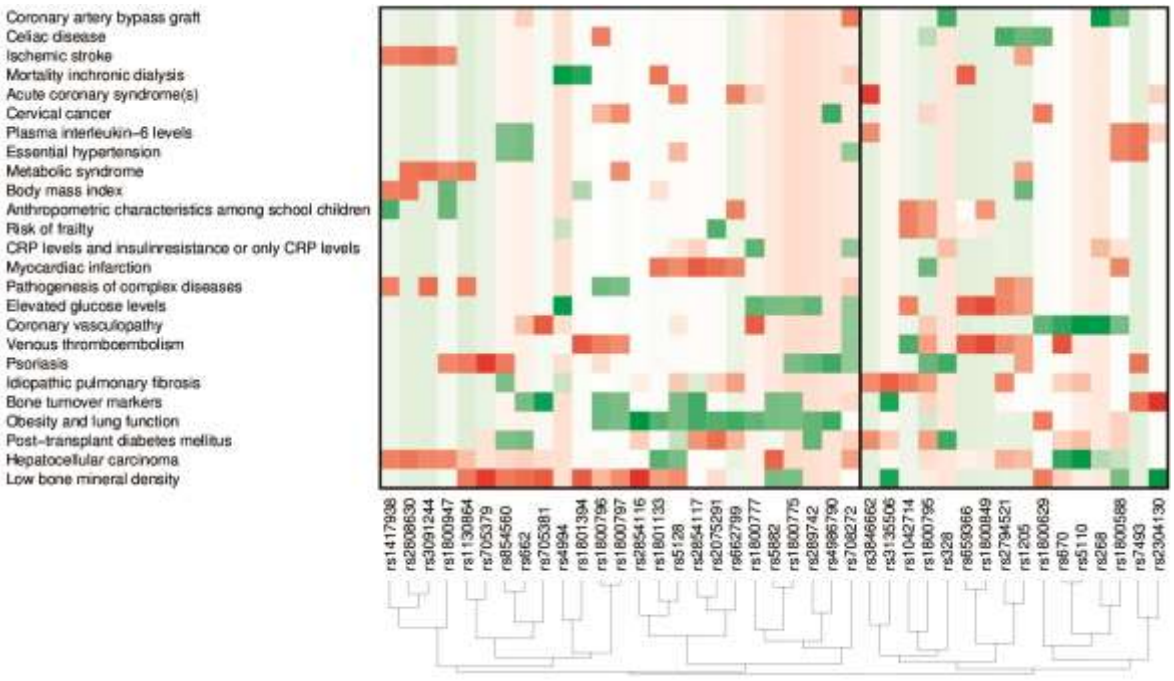
Figure Legend

Figure 1.

The positive or negative association of the SNPs of interest to diseases/conditions. Our analysis show that associations are generally unknown and when genes or SNPS are showing similar profiles those only rely on very few known associations. Note that SNPS are organised according to similarity in terms of condition associations. Rows show genes or SNPS of interest, whereas columns show conditions or condition groups.White block (or light green/red): no or unclear information regarding potential association. Green block: positive association. Red block: negative association. Shades of green and red show how strong the association is.



Tables

Table 1. Search criteria for gene and disease/ pathological condition association

Genes	Disease/Pathological condition: investigation of possible association
APOA1, APOA5, APOB, APOC3, APOE	Cardiovascular disease, Coronary heart disease, Coronary artery disease, Hypercholesterolemia
CETP	Cardiovascular disease, Coronary heart disease, Coronary artery disease, Hypercholesterolemia, Diabetes
GJA4 (CX37)	Atherosclerosis, Hypertension, Stroke, Coronary artery disease
HMGCR	Hepatic disease, Non- alcoholic fatty liver
LIPC	Hepatic disease, Hypercholesterolemia, Fatty acid metabolism
LPL	Dyslipidemia, CVD, Metabolic syndrome
PON1	Atherosclerosis, Diabetes, Metabolic syndrome
CAT	Diabetes, Hepatic diseases, Kidney diseases
GPX1	Various types of gastrointestinal cancer
GSTM1	Various types of gastrointestinal cancer, Various types of gastrointestinal disease, Coronary artery disease
GSTP1	Various types of gastrointestinal cancer, Various types of gastrointestinal disease, Coronary artery disease
GSTT1	Non-alcoholic fatty liver disease, Various types of gastrointestinal cancer, Various types of gastrointestinal disease, Coronary artery disease
MNSOD	Various types of gastrointestinal cancer, Coronary artery disease, Various types of gastrointestinal disease
SELS	Diabetes, Various types of gastrointestinal disease various types of gastrointestinal cancers, Metabolic risk factors
SOD2 & SOD3	Coronary Artery Disease, Chronic Obstructive Pumonary Disease
EPHX1	Chronic obstructive pulmonary disease, Various types of gastrointestinal cancer, CVD, Stroke
UCP2	Diabetes, Obesity, Abdominal obesity, Hyperinsulinemia
AGT	Coronary artery disease, Chronic kidney disease
CBS	Celiac disease, Hyperomocystenaemia, Homocysteine metabolism
COMT	Parkinson's disease, Schizophrenia
MTHFR	Homocysteine metabolism, Coronary artery disease, Cardiovascular disease, Coronary heart disease
MTR	Coronary artery disease, Rheumatoid arthritis
MTRR	Homocysteine metabolism, Coronary artery disease, Cardiovascular disease, Coronary heart disease, Reuhmatoid arthritis, Folate and choline metabolism

TCN2	To our knowledge there were no data that could be analysed at the moment that the metanalysis occured.
CRP	Body mass index, Obesity, Atrial fibrillation, Coronary heart disease, Diabetes, Inflammation/ Inflammatory response
IL-6	Coronary heart disease, Inflammation/ inflammatory response
TNF	Inflammation/Inflammatory response, Coronary artery disease, Weight regain, Acute pancreatitis, Gastric cancer and various types of gastrointestinal cancer
ADRB2	Hypertension, Acute coronary syndrome, Obesity, Cardiovascular diseases, Metabolic syndrome
ADRA2A	Ischemic stroke, Diabetes, Cardiovascular diseases, Obesity, Metabolic syndrome
ADRB1	Coronary heart disease, Diabetes, Obesity, Hypertension, Metabolic syndrome
ADRA1B	Coronary heart disease, Diabetes, Obesity, Hypertension, Metabolic syndrome
ADRB3	Coronary heart disease, Diabetes, Obesity, Hypertension, Metabolic syndrome
ADRA1A	Coronary heart disease, Diabetes, Obesity, Hypertension, Metabolic syndrome

Table 2. Number of studies showing incompatibility in all four models of analysis

	model 1 (conflicting association to conditions)	**model 1** (conflicting association to SNPs)	**model 2** (conflicting gene association to conditions)	**model 2** (conflicting association to genes)	**model 3** (SNPs per condition groups)	**model 4** (conflicting gene association to condition groups)	**model 4** (conflicting association to genes)
Incompatible results	31	29	17	31	NA	17	13
Compatible results	24	19	14	20	NA	13	3
Compatible results (very few studies per gene or SNP)	98	41	14	9	NA	14	NA

Please note that in option/model of analysis 3, no incompatibility was found. (NA, not available)

Table 3. An analytical representation of the incompatible results of genes with their respective nomenclature (and the rs numbers found in the studies researched) to condition groups, * «yes» or «no»

Gene	dbSNP id	condition groups with incompatible results (*)	number of studied condition groups	number of studies	average number of studies per condition group
IL6		11	12	176	14.7
CETP		8	11	118	10.7
ADRB3	rs4994	7	10	41	4.1
ADRB2		5	9	54	6.0
TNFA		5	9	65	7.2
CRP		4	13	111	8.5
APOA5		3	9	51	5.7
LIPC		3	8	29	3.6
APOC3		2	9	34	3.8
GSTP1	rs1695	2	4	12	3.0
LPL		2	8	22	2.8
MTHFR		2	11	34	3.1
PON1		2	9	45	5.0
UCP2		2	8	26	3.3
DGKB	rs2191349	1	1	2	2.0
MTRR	rs1801394	1	9	15	1.7
PON2		1	5	11	2.2

Table 4. Incompatibility of condition groups in relation to the genes, * «yes» or «no».

group number	group description	genes with incompatible results (*)	number of genes	number of studies	average number of studies/gene
GROUP 1	*Cardiovascular group (including ischemia and stroke)*	9	32	148	4.6
GROUP 4	*Metabolic syndrome, Diabetes and Insulin Resistance group*	8	26	171	6.6
GROUP 13	*Vascular group*	7	15	76	5.1
GROUP 17	*Other' group*	7	18	73	4.1
GROUP 3	*Obesity group*	5	16	88	5.5
GROUP 6	*Cancer group*	5	19	101	5.3
GROUP 7	*Bone disease group*	5	28	155	5.5
GROUP 10	*Gastrointestinal group*	4	7	26	3.7
GROUP 5	*Lung and Respiratory group*	3	19	47	2.5
GROUP 16	*Inflammation group*	3	9	46	5.1
GROUP 8	*Lipid group*	2	7	22	3.1
GROUP 12	*Nephrology group*	2	6	23	3.8
GROUP 11	*Anthropometry group*	1	11	23	2.1

Supplementary material

Supplementary Information

Meta-analysis of genes in commercially available nutrigenomic tests denotes lack of association with dietary intake and nutrient-related pathologies

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Supplementary Figure 1. Conflicting gene association to condition (incompatible results). Numbers next to the genes show the number of studies per gene.

Supplementary Figure 2. Conflicting associations to conditions (incompatible results). Numbers next to the genes show the number of studies per gene/SNP.

Supplementary Figure 3. Conflicting SNPs associations to links (incompatible results). The number of SNPs is shown vertically. The names of the links of diseases and conditions per SNP are shown horizontally.

Supplementary Figure 4. Conflicting gene associations to links (incompatible results). The number of genes is shown vertically. The names of the links of diseases' and conditions' groups per total number of genes are shown horizontally.

Supplementary Figure 5. Conflicting gene associations to links (incompatible results) to diseases and conditions. The number of genes is shown vertically. The names of the links of diseases and conditions are shown horizontally.

Supplementary Figure 6. Genes/SNPs and pathological conditions/diseases groups. The group names that correspond to the group numbers shown can be found in suppl. figure 1. The black colour shows no statistical association between the SNPs and the pathological conditions/diseases groups.

Supplementary Figure 7. Conflicting results (number of studies) for the *APOA5*, *CETP*, *IL6* and *MTHFR* genes and their link to CAD (n=17929, 18: «yes», 14: «no», 4: «may»).

Supplementary Figure 8. Conflicting results (number of studies) for the *PON1, LIPC* and *CETP* genes and their link to CHD (coronary heart disease) (n=6119, 6: «yes», 9: «no», 4: «may»).

Supplementary Figure 9. Conflicting results (number of studies) for *CRP, LIPC* and *IL6* genes and their link to CVD (n=31527, 21: «yes», 4: «no», 12: «may»)

Supplementary Figure 10. Conflicting results (number of studies) for the *CRP* and *IL6* genes and their link to CRP levels and insulin resistance or only CRP levels (n=4199, 5: «yes», 5: «no»).

Supplementary Figure 11. Conflicting results (number of studies) for the *ADRB3, APOA5, APOC3* and *CRP* genes and their link to triglycerides (n=28528, 24: «yes», 10: «no», 11: «may»).

Supplementary Figure 12. Conflicting results (number of studies) for the *ADRB3* and *CRP* genes and their link to obesity (n=3809, 3: «yes», 5: «no»).

Supplementary Figure 13. Conflicting results (number of studies) for the *UCP2* and *CETP* genes and their link to BMI (n=2753, 2: «yes», 9: «no», 1:«may»).

Supplementary Figure 14. Conflicting results (number of studies) for the *ADRB2* and *UCP2* genes and their link to diabetes (n=3131, 4: «yes», 3: «no»,)

Supplementary Figure 15. Conflicting results (number of studies) for the *ADRB2* and *UCP2* genes and their link to HDL-C (n=43989).

Supplementary Figure 16. Conflicting results (number of studies) for the *ADRB2* and *UCP2* genes and their link to metabolic syndrome (n=4599, 2: «yes», 9: «no»).

Supplemenary Figure 17. Conflicting results (number of studies) for the *LIPC* gene and its link to total cholesterol (n=8583, 2: «yes», 6: «may»).

Supplementary Figure 18. Conflicting results (number of studies) for the *ADRB2* gene and its link to total fat (n=1250, 1: «yes», 3: «no»)

Supplementary Figure 19. Conflicting results (number of studies) for the *ADRB2* and *ADRB3* genes and their link to subcutaneous fat distribution (n=1509, 2: «yes», 4: «no»).

Supplementary Figure 20. Conflicting results (number of studies) for the *ADRB2* and *ADRB3* genes and their link to abdominal adiposity (n=2446, 2: «yes», 4: «no»).

Supplementary Figure 21. Conflicting results (number of studies) for the *ADRB2* gene and its link to hypertension (n= 8643, 2: «yes», 4: «no»).

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Websites

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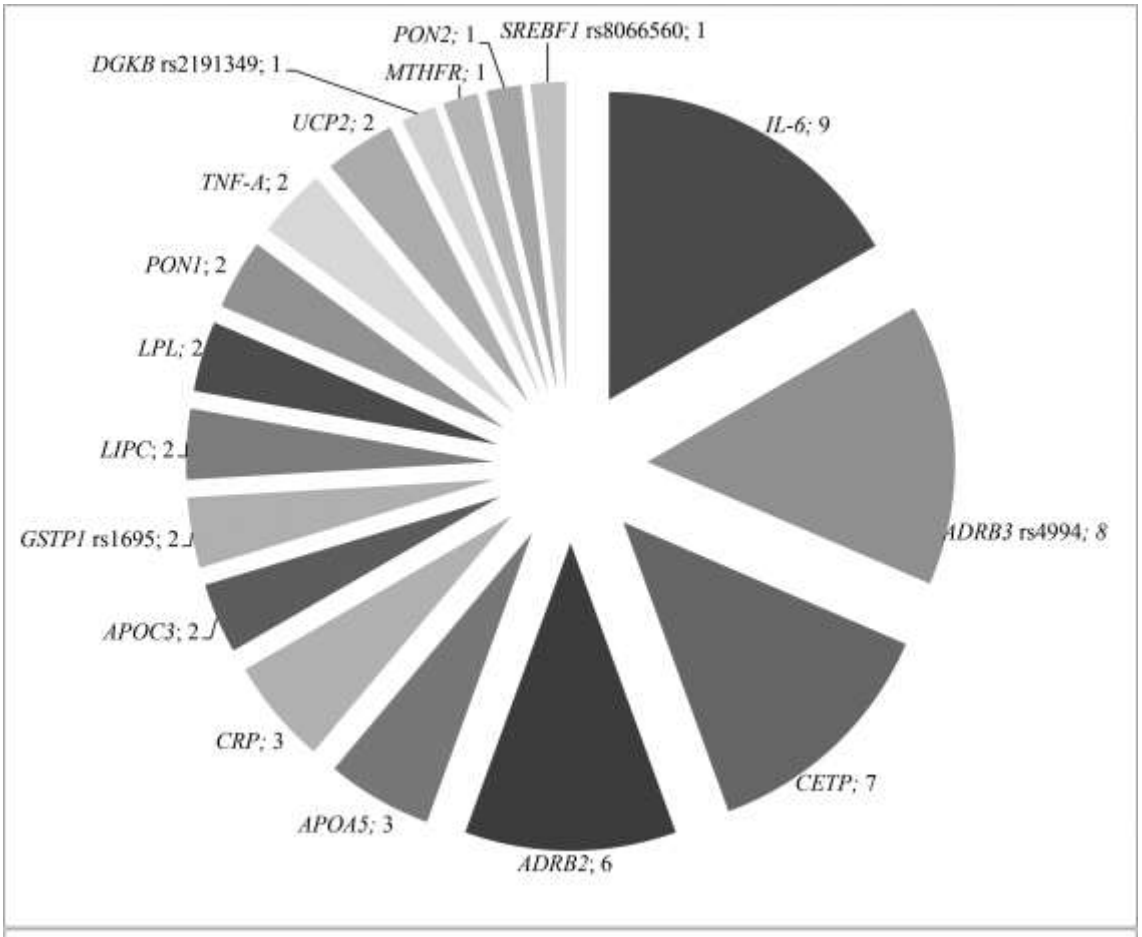
Supplementary figures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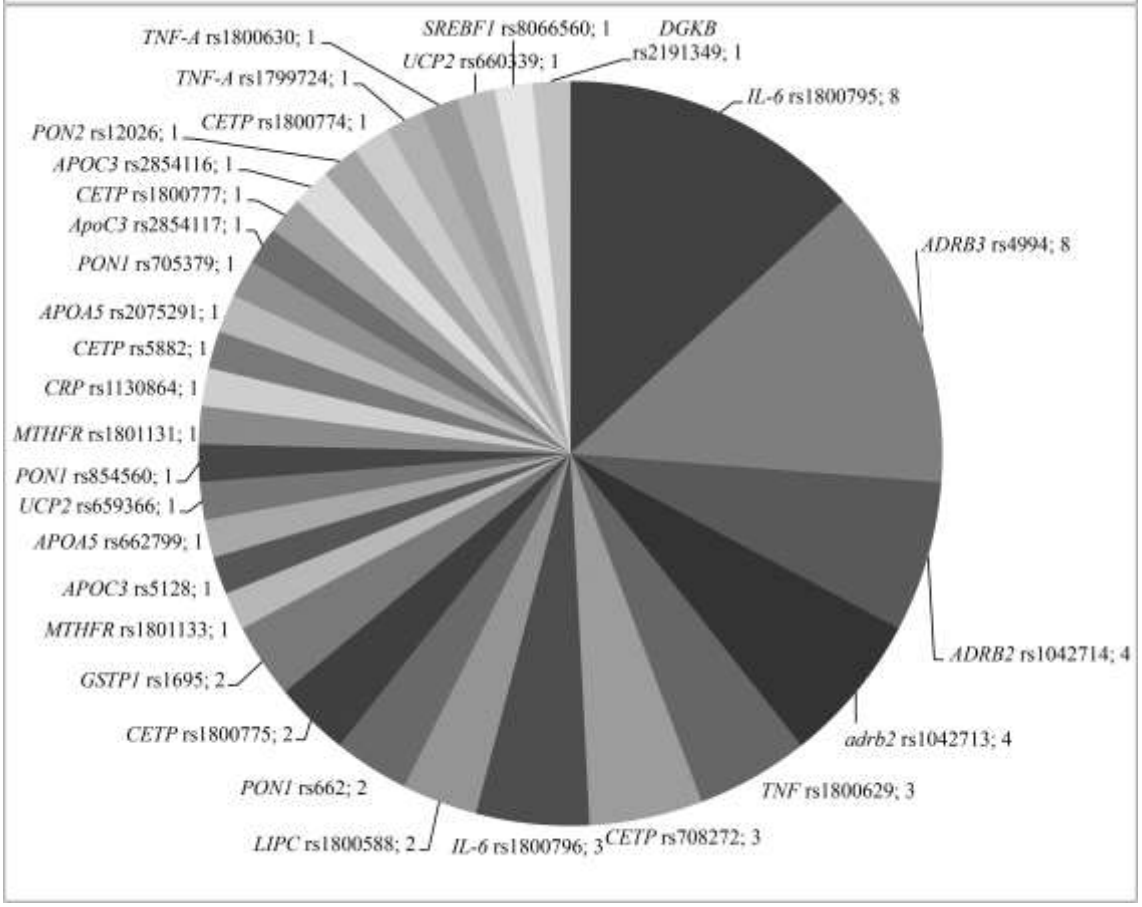
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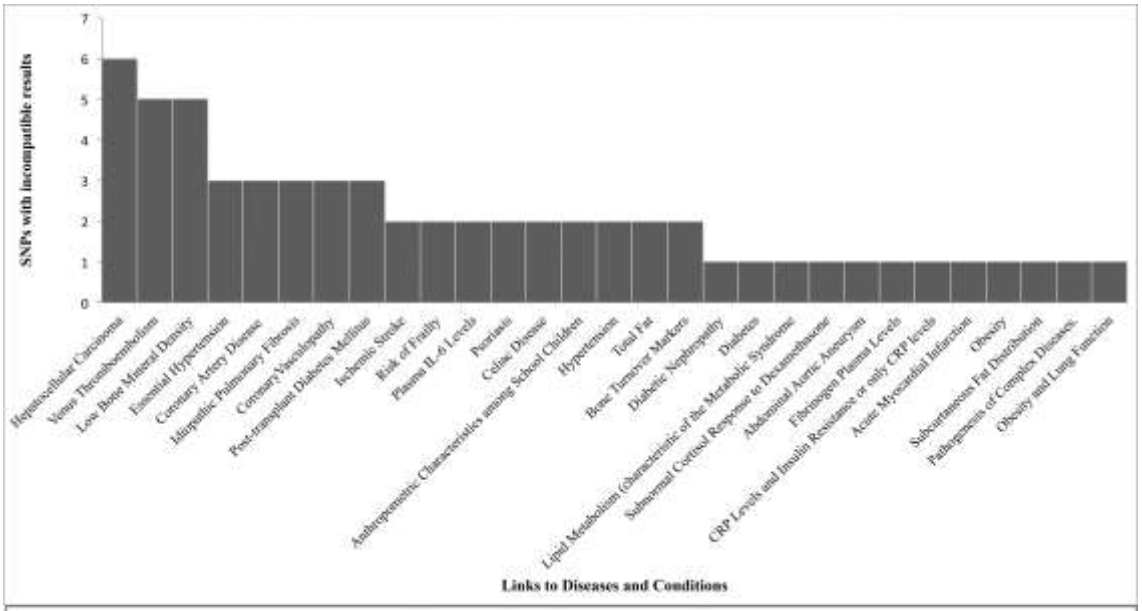
SNPs with incompatible results
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Coronary Artery Disease
Idiopathic Pulmonary Fibrosis
Coronary Vasculopathy
Post-transplant Diabetes Mellitus
Ischemic Stroke
Risk of Frailty
Plasma IL-6 Levels
Psoriasis
Celiac Disease
Anthropometric Characteristics among School Children
Hypertension
Total Fat
Bone Turnover Markers
Diabetic Nephropathy
Diabetes
Lipid Metabolism (characteristic of the Metabolic Syndrome
Subnormal Cortisol Response to Dexamethasone
Abdominal Aortic Aneurysm
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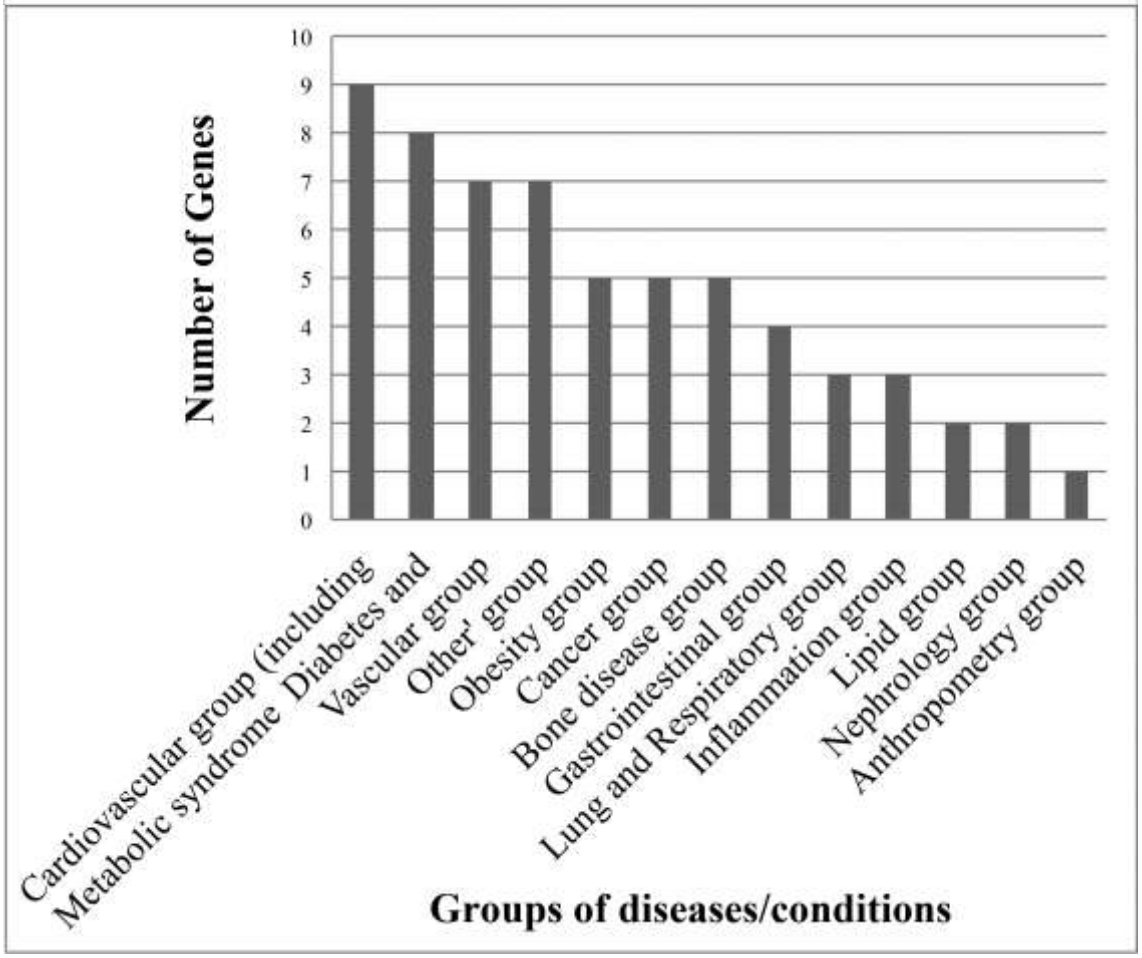
Obesity
Subcutaneous Fat Distribution
Pathogenesis of Complex Diseases
Obesity and Lung Function
Links to Diseases and Conditions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Cardiovascular group (including Metabolic syndrome
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Other' group
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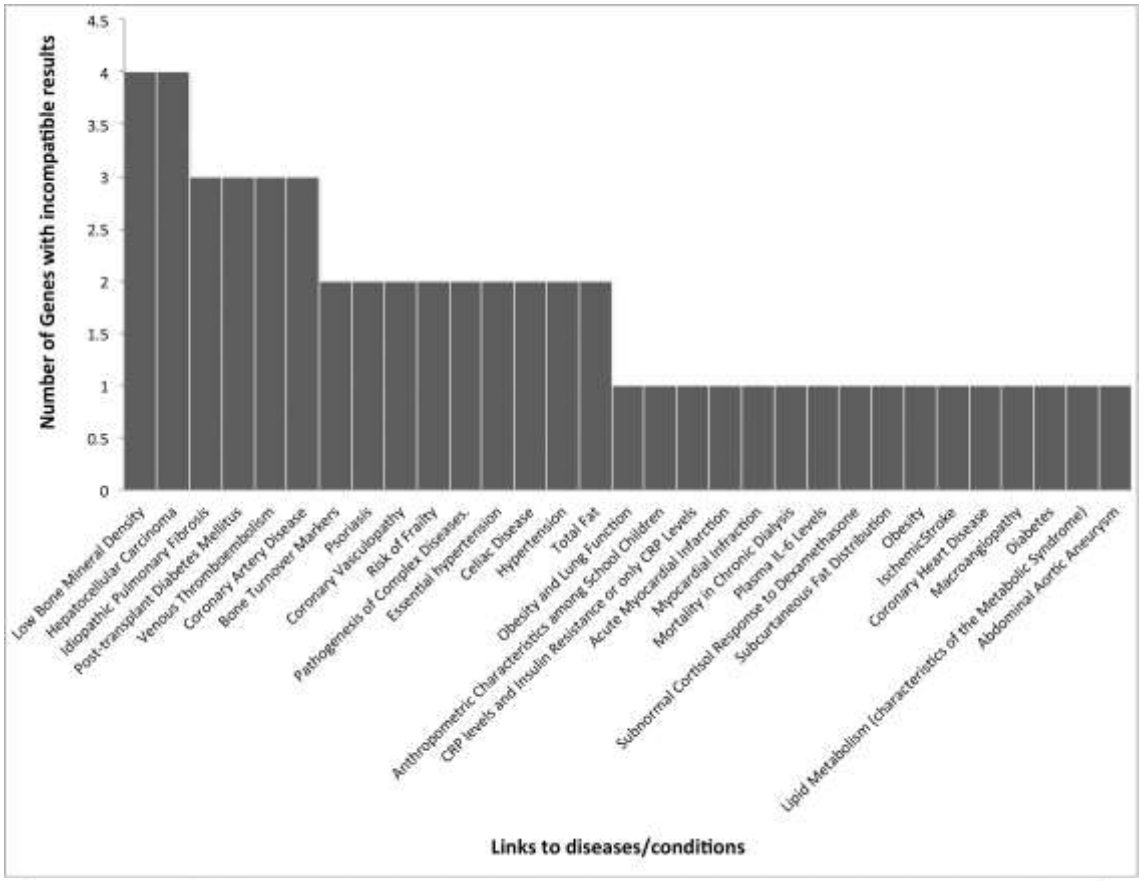
Gastrointestinal group
Lung and Respiratory group
Inflammation group
Lipid group
Nephrology group
Anthropometry group
Groups of diseases/conditions



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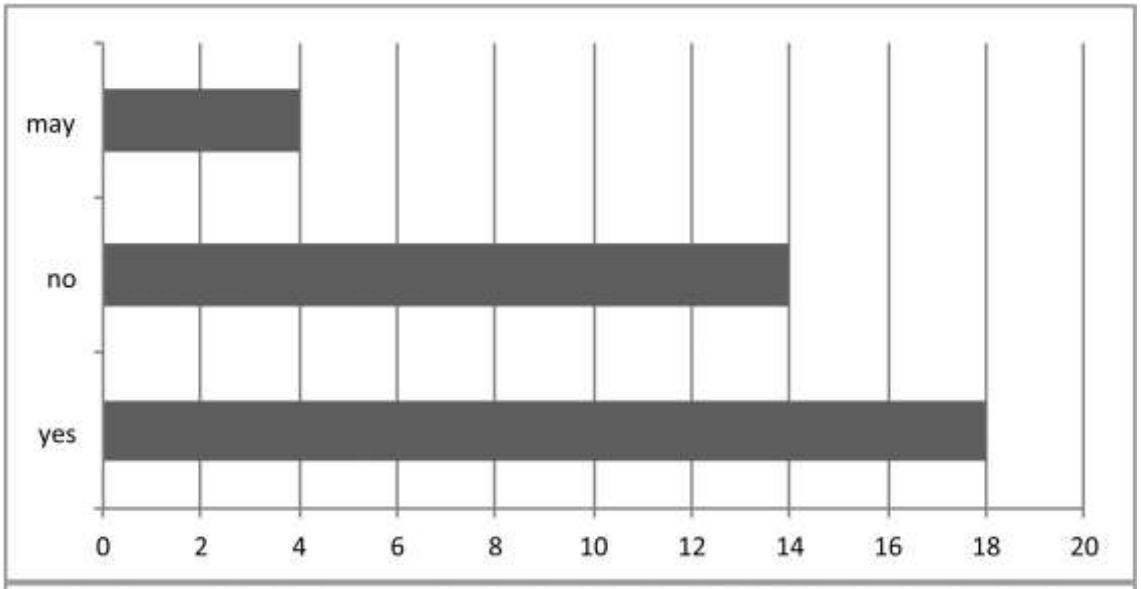
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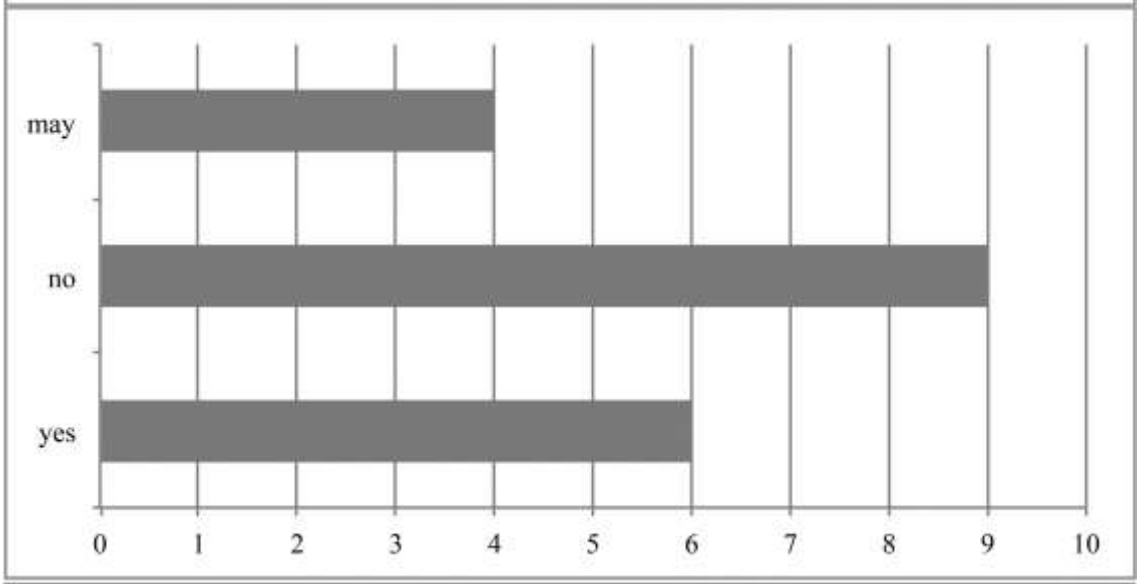
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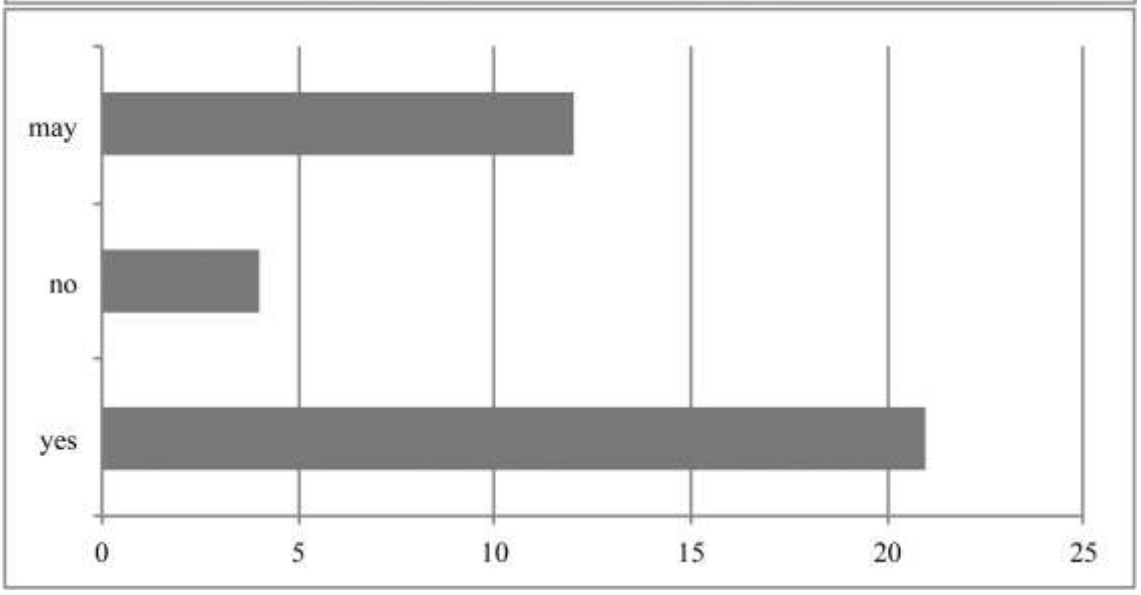
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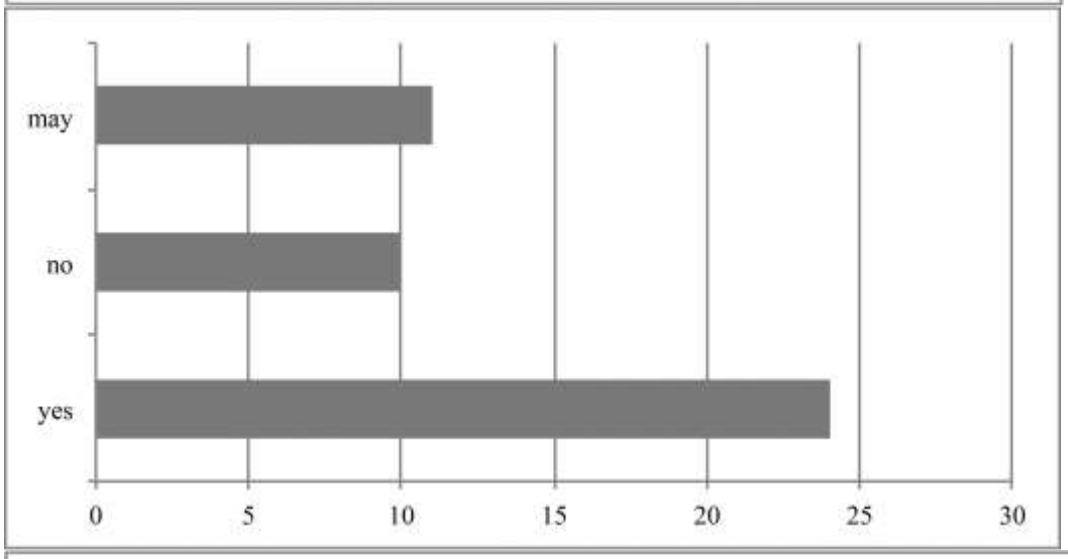
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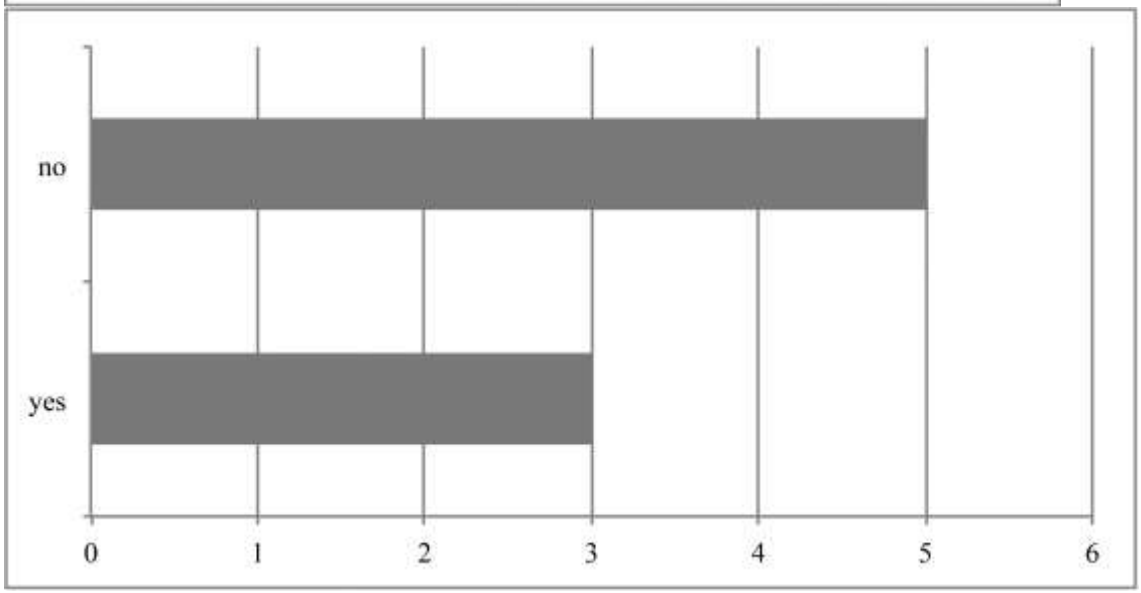
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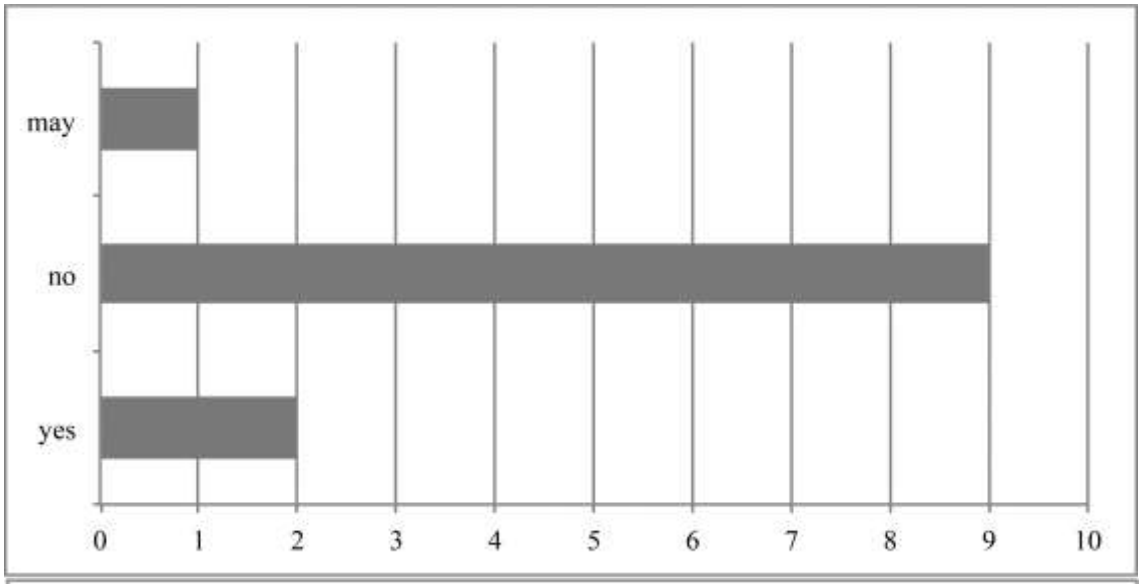
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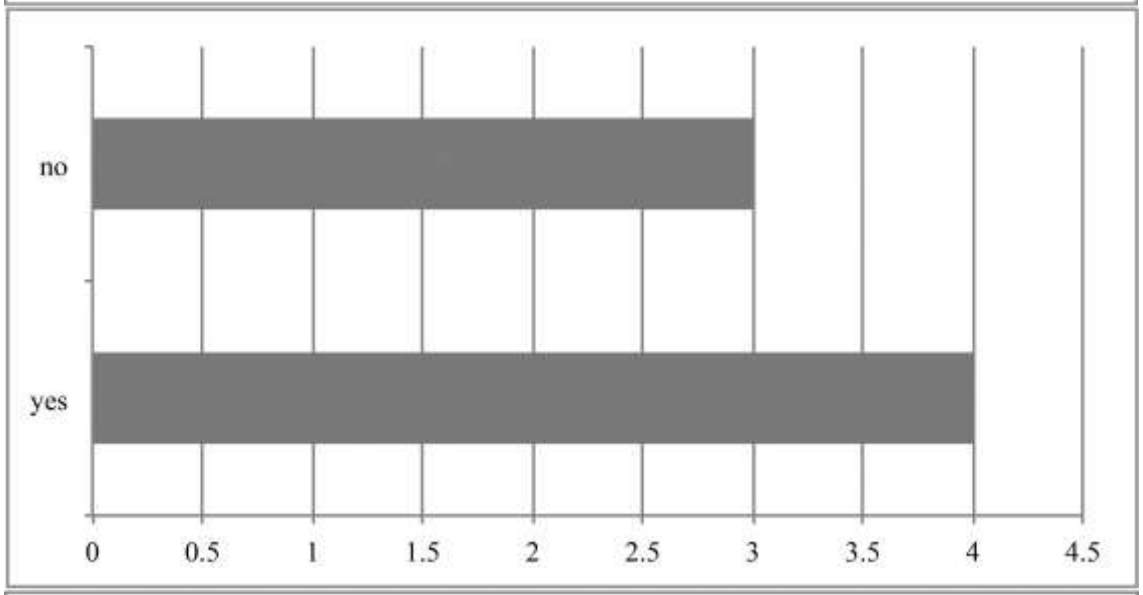
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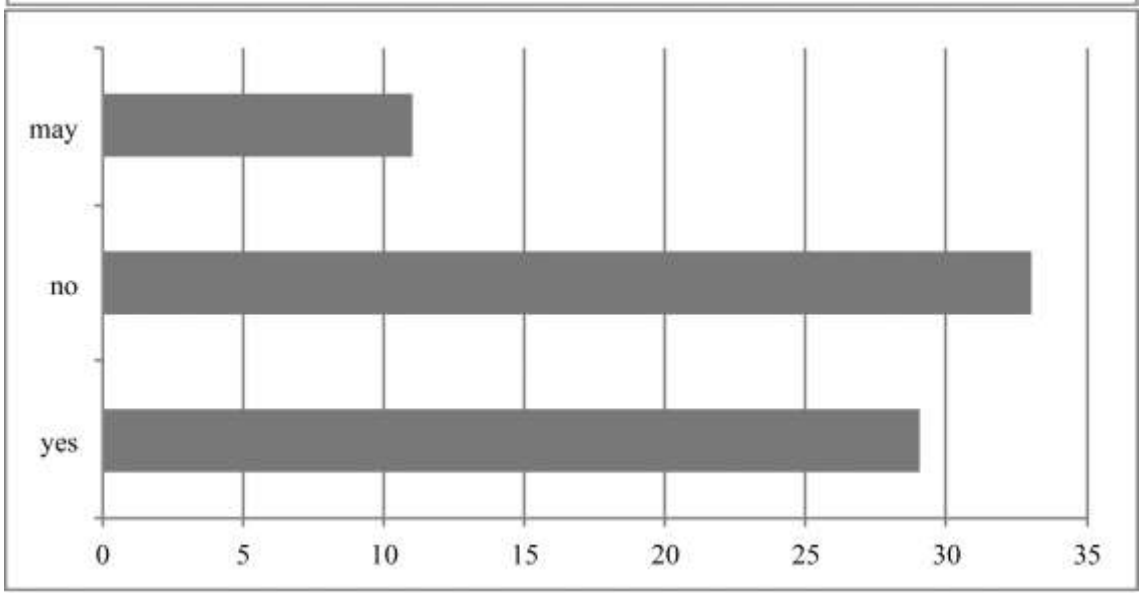
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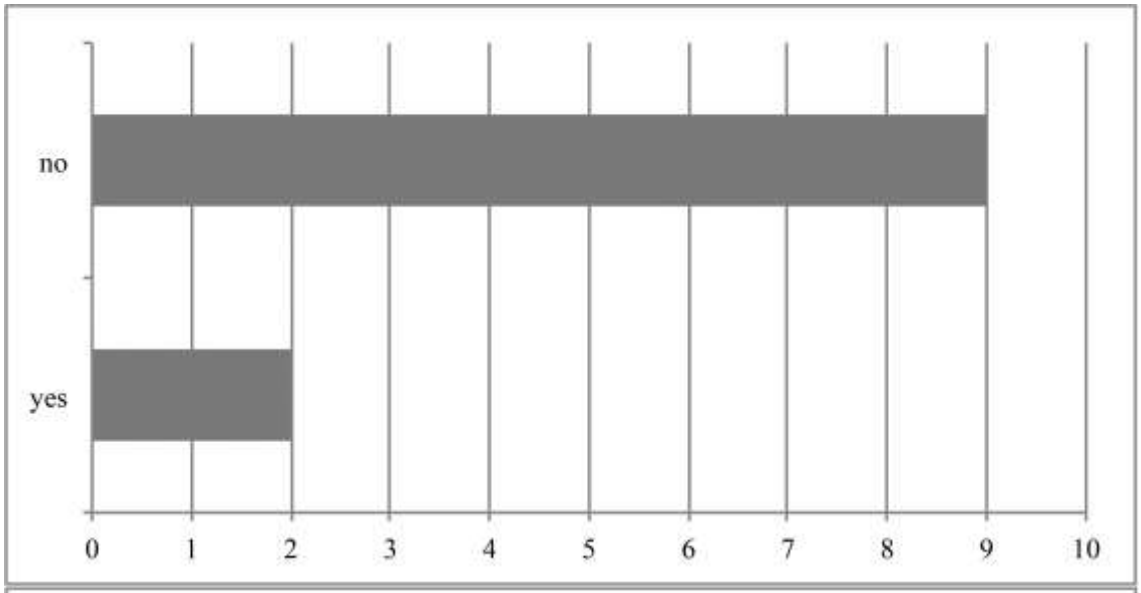
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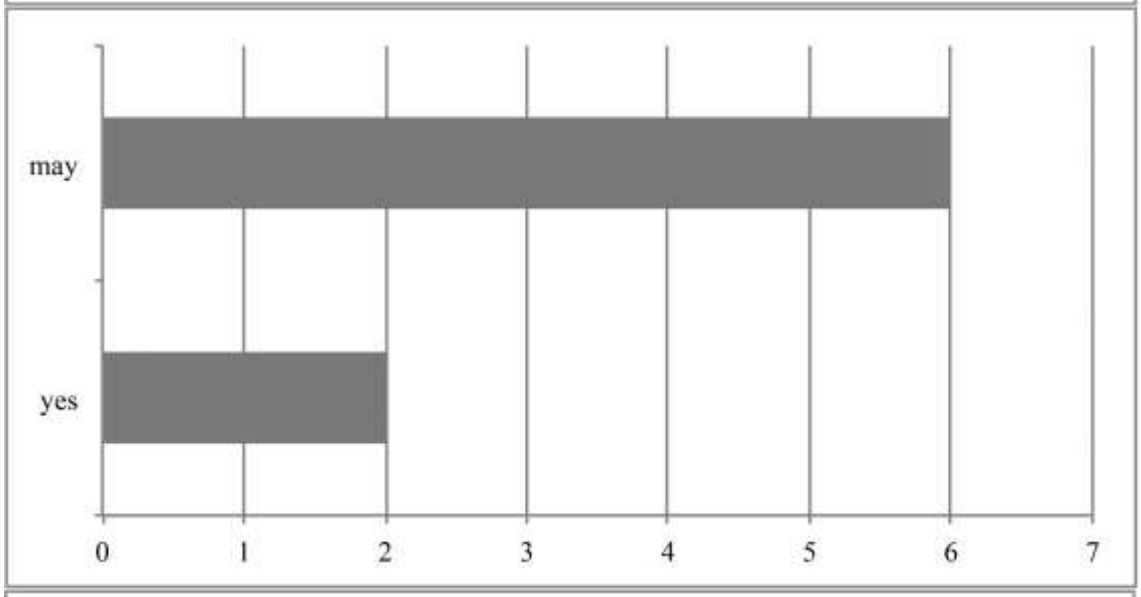
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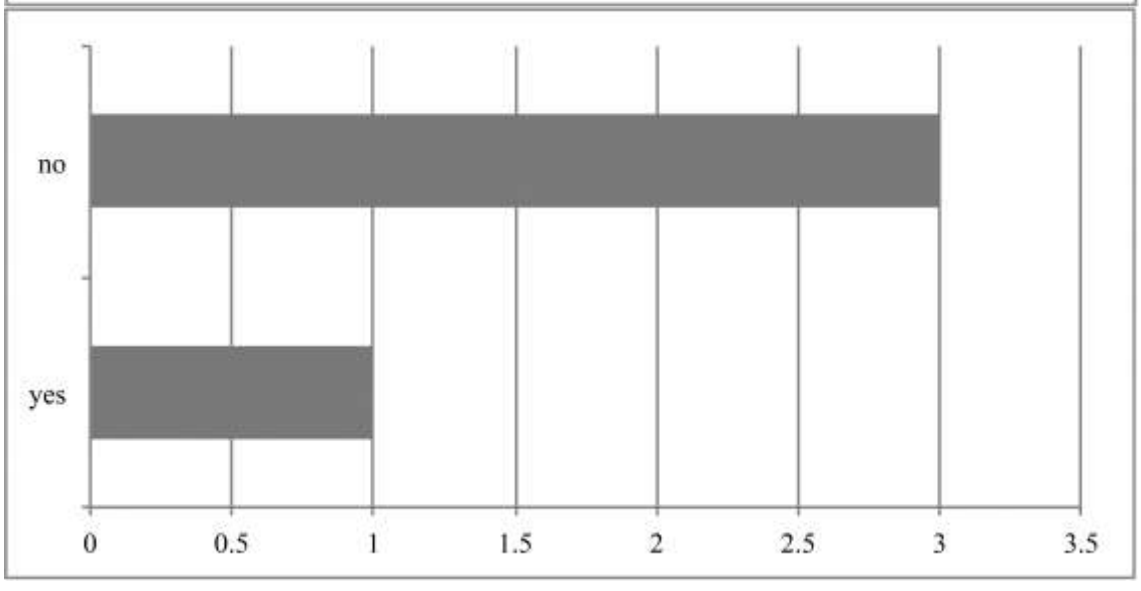
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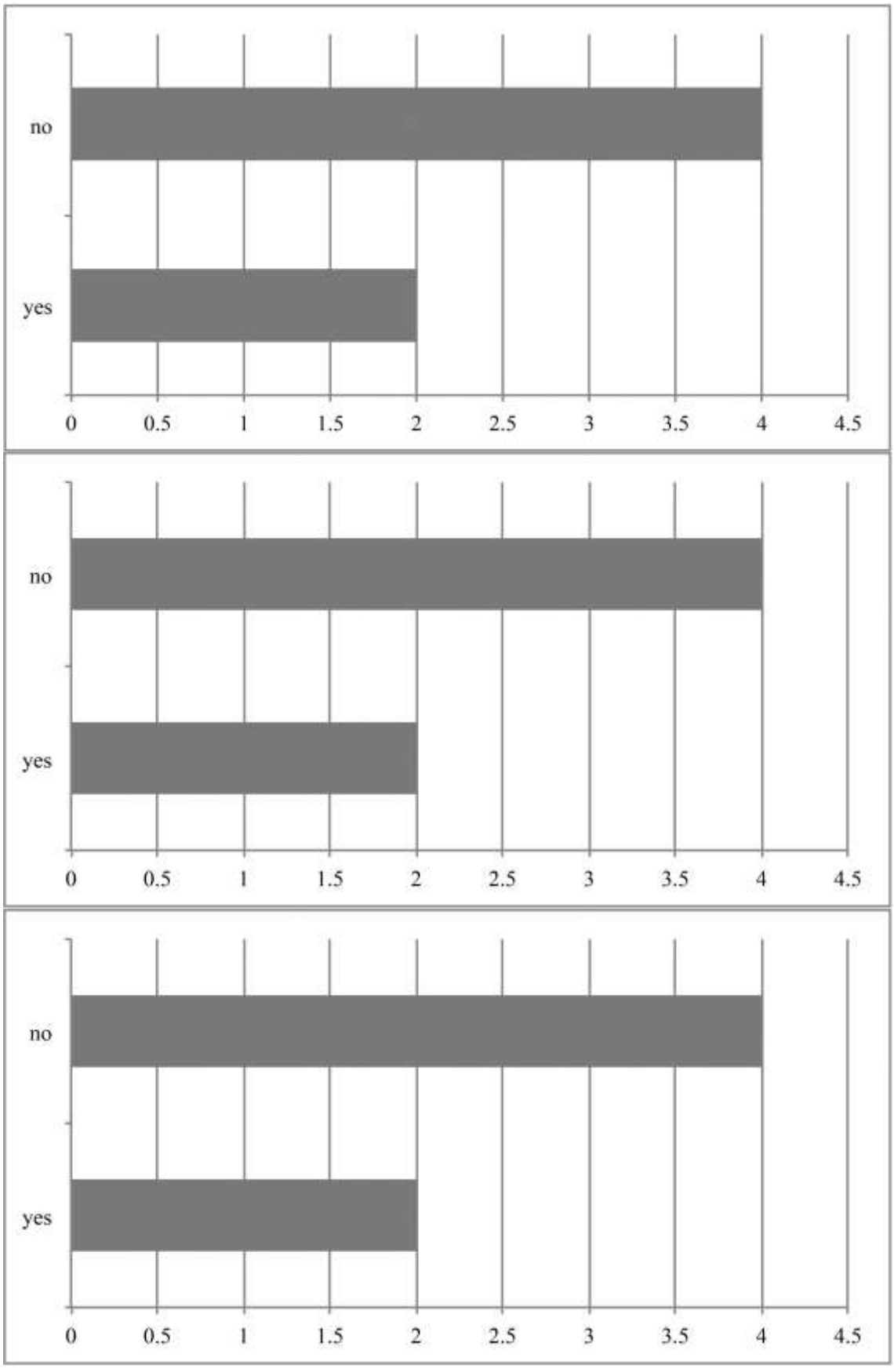
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