

DIET AND SEMEN QUALITY IN HEALTHY MALES FROM THE POPULATION OF THE LOWER SILESIA REGION IN POLAND (THE ANDROLS STUDY)

By Anna Książek¹, Aleksandra Zagrodna¹, Małgorzata Słowińska-Lisowska¹, Paweł Józków¹, Felicja Lwow², Marek Mędraś¹

¹Department of the Biological and Motor Basis of Sport, University School of Physical Education, Wrocław, Poland.

²Department of Health Promotion, University School of Physical Education, Wrocław, Poland.

Corresponding Author Anna Książek: anna.ksiazek@awf.wroc.pl

Submitted: November 13, 2017. Accepted: January 16, 2018. Published: January 29, 2018.

ABSTRACT

Background

Numerous studies have shown the associations between different dietary patterns and semen quality in a male population. There is no evidence on the relationship between dietary intake and markers of male fertility potential. The aim of this study was to investigate the relationship between dietary nutrients intake and semen quality parameters among healthy men from Lower Silesia (a region of Poland).

Methods

We enrolled 177 healthy young men aged 18–35 years from a genetically homogenous population of Lower Silesia (a region of Poland). Those who responded to the invitations were asked to complete the questionnaires covering: medical history and nutritional habits (last 5-day recall diary). The semen samples were analyzed with use of the Sperm Class Analyser.

Results

The results showed a statistically significant positive correlation between the intake of saturated, monounsaturated fatty acids and immotility. The results also demonstrated a statistically significant positive correlation between energy derived from fat and immotility and rapid (a) and slow (b) progressive motility. As well, a statistically negative correlation between the energy value of the diet and sperm concentration, energy derived from the consumption of carbohydrates and semen volume, consistency and the energy derived from the consumption of fat and sperm consistency and immotility was shown.

Conclusion

Based on our studies we concluded that further research is needed to confirm these findings and extend these results to other populations.

Some of the factors that may affect fertility include: body weight, dietary patterns, alcohol consumption, smoking, environmental pollution, past infections, current illnesses, medications, and family medical history. It has also been demonstrated that excessive use of tobacco, heavy alcohol intake, marijuana use, cocaine use, regular exposure to high temperatures such as in sauna are risk factors for decreased sperm quality.¹⁻³ Little is, however, known about the exact ways in which the nutrients can influence male reproductive potential.³ There are reports in the literature of the adverse impact of certain dietary ingredients (carbohydrates, saturated fatty acid, trans fatty acid) on semen quality.⁴⁻⁶ Other studies have demonstrated that specific nutritional factors can favourably affect semen quality (vitamin C, vitamin E, β -carotene).⁷⁻⁹ To date, nutritional studies on semen quality in men have mostly focused on dietary patterns or food groups. Some studies have demonstrated that a “western pattern” diet, which is organ meats, red and processed meats, sugar, soft drinks and confectionary, pasta, rice and refined grains, potatoes, fried and fast foods, high-fat dairy products, hydrogenated fats, mayonnaise and fatty sauces, and snacks, might have a negative effect on male fertility, other recent studies have also indicated that a “prudent pattern” diet, in which more leafy green vegetables, yellow vegetables, other vegetables, tomatoes, fish and other seafood, fruits and natural fruit juices, legumes, whole grains, poultry, tea and coffee, low-fat dairy products, and vegetable oils are consumed, may benefit sperm quality.¹⁰⁻¹² Based on the available literature in PubMed, no study has been performed to assess the impact of the quantities of selected dietary nutrients on semen quality.

The aim of this study was to investigate the relationship between energy value, intakes of nutrients, minerals, vitamins, dietary fibre, water, caffeine in daily food rations and semen quality parameters among healthy men from Lower Silesia (a region of Poland).

METHODS

Subjects

We performed the investigation in 177 healthy young men aged 18–35 years from a genetically homogenous population of Lower Silesia (a region

of Poland). The anthropometric characteristics of the study group is presented in Table 1. We announced the study through: fliers, notices, messages (via Facebook, Twitter, Instagram) and personal communication to university students, societies and clubs from the region.

Those who responded to the invitations were asked to complete the questionnaires covering: medical history and nutritional habits (last 5-day recall diary). The final stage consisted in the collection of blood and sperm samples during scheduled visits.

We did not enrol subjects who: were being evaluated or treated for male reproductive system pathologies, who had undergone urogenital surgery, who had known or suspected fertility problems, or who had received medications that could interfere with semen evaluation. During the dietary pattern assessment, the males did not take any food supplements that could affect the assessment results.

The study was approved by the Bioethics Committee of the University School of Physical Education, Wroclaw, Poland (resolution number 36/2013).

Food Diary

The subjects' diets were assessed by the 5-day recall method, including one Sunday each, using the software Dieta 5.0.¹³ The subjects were instructed how to fulfill food diary. The participants self-reported all the consumed foods and fluids. The subjects provided information about the times, types and quantitative structures of their meals and beverages they consumed. The quantities of all the food/beverages items were reported in household measures or, if available, according to packaging details.

We analyzed the energy values and the contents of nutrients, minerals (sodium, calcium, potassium, phosphorus, magnesium, iron, zinc, copper, manganese, iodine), vitamins (A, β -carotene, B₁, B₂, B₃, B₆, B₁₂, folic acid, C, D, E), dietary fibre and water in the diets of the healthy men.

Collection of semen for diagnostic testing and semen analysis was in line with the most recent World Health Organisation guidelines.¹⁴

Semen Analysis

Semen samples were collected in a room adjacent to the andrology laboratory. The samples were obtained by masturbation, ejaculated into sterile plastic

TABLE 1 Demographic Characteristics of the Study Population

	Total (n=177)
Age (years)	24.8 ± 3.8
BMI (kg/m ²)	24.0 ± 2.9
WHR	0.9 ± 0.1
Current smoker, n (%)	25 (14.1)
Semen volume (mL)	3.2 ± 2.1
Sperm concentration (10 ⁶ /mL)	57.59 ± 44.9
Total sperm count (millions)	163.3 ± 137.8
Rapid (a) progressive motility (%)	22.0 ± 11.4
Slow (b) progressive motility (%)	13.0 ± 8.9
Progressive motility (grades a+b, %)	35.2 ± 14.5
Immotility (%)	45.6 ± 17.4
Vitality (%)	59.3 ± 16.6

BMI = body mass index; WHR = waist-to-hip ratio.

(non-toxic for spermatozoa) container and placed in an incubator (37°C) during liquefaction.

The ejaculation abstinence time and the time between sample collection and analysis were recorded in the subject's personal lab report.

All the semen samples were analyzed by a single experienced medical analyst according to the WHO 2010 guidelines manually and with use of the Sperm Class Analyser [SCA] (CASA System MICROPTIC S.L., Barcelona, Spain). The performance of the laboratory is continually evaluated in an external quality assessment scheme (EQAS Labquality, Helsinki, Finland; www.labquality.fi).

Semen analysis included the measurements of pH, concentrations of spermatozoa in semen, peroxidase-positive cells, and the evaluation of sperm motility, vitality and morphology.

Semen volume was estimated by weighing method (where 1 g was assumed to correspond to 1 mL). Semen pH was measured with pH indicator strips (Merck, Germany). Motility of spermatozoa was evaluated by

computer-aided sperm analysis (SCA). The procedure is performed at 37°C using a heated microscope stage. Sperm movement was graded as: rapid (a) and slow progressive (b) motility, non-progressive motility, immotility. The number of spermatozoa was assessed with SCA and verified manually with use of the improved Neubauer haemocytometer (examination with a microscope equipped with phase-contrast optics at 400× magnification). The eosin-nigrosin staining (VitalScreen test, FertiPro N.V., Belgium) was used for the assessment of the vitality of spermatozoa. Each slide was examined with a microscope equipped with bright-field optics at 1000× magnification in oil immersion. Test LeucoScreen (FertiPro N.V., Belgium) was applied to detect peroxidase-positive leucocytes with use of the improved Neubauer chamber (evaluation with a microscope equipped with phase-contrast optics at 400× magnification).

Sperm morphology was evaluated with use of computer-aided sperm analysis (SCA), verified manually (Diff-Quik staining method, MICROPTIC S.L.,

Barcelona, Spain). The examinations were performed with a bright-field objective at 1000×magnification in oil immersion.

Statistical Analysis

Associations between the variables were investigated by calculating the partial correlation coefficient, controlling for the other variables (body mass index [BMI], waist-to-hip ratio [WHR]), alcohol intake, smoking, carrying a mobile phone in a trouser pocket, working with a laptop on one's knees, wearing tight clothing, going to a sauna, caffeine intake, β -carotene intake). Outliers were rejected. Non-normally distributed variables were analyzed using the Box-Cox transformation.

Associations between the variables were evaluated using the two-sided Pearson coefficient of correlation (also for dichotomous variables). In the second part

of the analysis the associations were evaluated with adjustments for: BMI, WHR, alcohol intake (yes/no), smoking (yes/no), carrying a mobile phone in a trouser pocket (yes/no), working with a laptop on one's knees (yes/no), wearing tight clothing (yes/no), going to a sauna (yes/no), caffeine intake (expressed in mg/day). Associations between the variables were checked by evaluating the significance of the partial correlation coefficient with adjustment for other variables. Associations at the level of $p \leq 0.05$ were assumed to be statistically significant.

RESULTS

The demographic and dietary characteristics of the subjects are shown in Tables 1 and 2.

Based on the analysis of the associations between the diet ingredients and semen parameters a significant ($p \leq 0.05$) negative correlation was shown between the

TABLE 2 Dietary Characteristics of the Study Population

	Total (n=177)
Calorie intake (kcal/day)	2649.9 \pm 663.3
Carbohydrate intake (g/day)	333.8 \pm 98.1
Carbohydrate intake (% energy)	49.4 \pm 7.4
Fibre intake (g/day)	25.1 \pm 11.0
Protein intake (g/day)	124.1 \pm 46.2
Protein intake (% energy)	18.4 \pm 4.1
Fat intake (% energy)	32.6 \pm 7.1
Saturated fatty acid intake (g/day)	33.7 \pm 12.8
Saturated fatty acid intake (% energy)	11.4 \pm 3.0
Monounsaturated fatty acid intake (g/day)	38.3 \pm 14.2
Polyunsaturated fatty acid intake (g/day)	19.0 \pm 10.0
Sucrose intake (g/day)	51.5 \pm 29.4
β -Carotene intake (μ g/day)	4954.8 \pm 4247.8
Caffeine intake (mg/day)	95.8 \pm 78.3
Water intake (mL/day)	2005.3 \pm 992.5

mean energy value of the daily food ration and the mean sperm count [$10^6/\text{mL}$] (Table 3).

A significant negative correlation was shown between the percent intake of energy provided by fats in the average food ration and both semen consistency ($p \leq 0.05$) and immotility ($p \leq 0.01$). A significant positive correlation was shown between the percentage intake of energy provided by fats and the following parameters: rapid (a) progressive motility ($p \leq 0.05$), slow (b) progressive motility ($p \leq 0.01$) and sperm vitality ($p \leq 0.05$) (Table 3).

A significant negative correlation was shown between the percent intake of energy provided by carbohydrates and both semen consistency ($p \leq 0.05$) and semen volume ($p \leq 0.05$).

The analysis of the results also showed a significant negative correlation between the quantity of saturated fatty acids in the daily food ration and immotility ($p \leq 0.05$). The average daily consumption of monounsaturated fatty acids was shown to negatively correlate in a significant manner with immotility ($p \leq 0.05$). No significant correlation was found between the polyunsaturated fatty acids and semen quality (Table 3).

No significant associations were found between the average daily consumption of protein, vitamins (A, β -carotene, B₁, B₂, B₃, B₆, B₁₂, folic acid, C, D, E), minerals (sodium, calcium, potassium, phosphorus, magnesium, iron, zinc, copper, manganese, iodine), dietary fibre, caffeine and semen parameters (semen volume, consistency, total sperm count, sperm concentration, sperm motility, rapid [a] and slow [b] progressive motility, immotility, vitality).

DISCUSSION

The study demonstrated that human nutrition can impact semen quality and male fertility.^{6,15}

Examining the association between energy intake and semen quality in the male subjects a significant negative correlation was shown between the energy value of the diet and sperm concentration ($10^6/\text{mL}$). High calorie intake can therefore negatively impact the sperm count. Other studies have demonstrated that excessive body weight, which is determined to a considerable degree by dietary habits, can adversely affect semen quality causing lower sperm concentration, semen volume and total sperm count.^{16,17}

TABLE 3 Associations between the Diet Ingredients and Semen Parameters Evaluated in the Study

	Semen volume [mL]	Consistency	Total sperm count ($\times 10^6$)	Sperm concentration ($10^6/\text{mL}$)	Rapid (a) progressive motility (%)	Slow (b) progressive motility (%)	Immotility (%)	Vitality (%)
Energy [kcal]	0.034	0.054	-0.205	-0.218*	-0.012	0.045	0.001	0.003
Fat [% energy]	0.194	-0.227*	0.090	0.090	0.265*	0.244*	-0.346**	0.250*
Carbohydrate [% energy]	-0.241*	-0.213*	-0.076	-0.076	-0.149	-0.193	0.201	-0.175
Saturated fatty acids [g]	0.155	-0.126	-0.018	-0.081	0.158	0.173	-0.240*	0.165
Monounsaturated fatty acids [g]	0.171	-0.123	-0.002	-0.105	0.217	0.176	-0.244*	0.176

Statistical significance levels: * $p < 0.05$, ** $p < 0.01$.

The present study showed a significant negative correlation between the percent carbohydrate content of the daily food ration and both semen volume and consistency. Liu et al.¹⁰ showed that a diet referred to as the high-carbohydrate diet (assessed by using questionnaire included the frequency and amount of consumption for each food group) negatively impacted semen quality of the subjects (abnormal total sperm count and progressive motility). The same study demonstrated that males who consumed large amounts of highly sweet snacks and sugar-sweetened drinks had lower sperm counts ($10^6/\text{mL}$). There have also been reports that suggest a possible relationship between high-carbohydrate diet and asthenozoospermia. It was pointed out that an increased intake of sweet food was significantly associated with a higher risk of asthenozoospermia.¹⁸ It should be emphasized that products rich in refined sugars are considered to be dietary elements that decrease semen quality and increase the risk of asthenozoospermia. In contrast to fruits and vegetables, which are rich in minerals and antioxidants and fibre, all of which may have a pivotal role in improving semen quality.¹⁹

The present study showed that the percent intake of energy provided by fats significantly positively correlated with vitality and with rapid progressive motility and strongly positively correlated with slow progressive motility and strongly negatively correlated with immotility and significantly negatively correlated with sperm consistency. When examining the associations between the diet and semen quality in a group of 99 males aged 18 to 55 years, Attaman et al.²⁰ has demonstrated that total fat intake was negatively related to total sperm count and sperm concentration. It should, however, be noted that these associations appeared to be driven primarily by the intake of saturated fat. Of note is the fact that our quantitative analysis of the food rations consumed by our subjects showed that the percentage of unsaturated fats predominated in the total amount of dietary fat (average daily intake: 33.7 g for saturated and 57.3 g for unsaturated fats).

The present study also showed that the intake of monounsaturated fatty acids significantly negatively correlated with immotility. Alizadeh et al.²¹ reported that in mammalian biological systems, as observed in spermatozoa, C18:1 n-9 is a major fatty

acid among monounsaturated fatty acids (MUFAs). Polyunsaturated fatty acids (PUFAs) have also been reported to significantly affect spermatogenesis. The increase in the relative amount of PUFAs appears to be mediated to a great extent by local fatty acid metabolism, as evidenced by the high efficiency of Sertoli cells converting 18-carbon PUFAs into 22- and 24-carbon PUFAs as well as the high expression levels of the enzymes necessary for this metabolic process, including D5- and D6-desaturase and fatty acid elongases in the testis and epididymis, affecting spermatogenesis.²¹ The present study did not confirm the association between polyunsaturated fatty acid intake and semen quality.

The present study also demonstrated a significant negative correlation between the intake of saturated fatty acids and immotility, although no significant associations were shown with the other semen quality parameters. Chavarro et al.²² on the other hand, found a positive association between stearic acid intake and sperm motility. Similar results were reported by Vujkovic et al.,⁵ who assess the effects of the traditional Dutch dietary pattern (high in meat products, an important source of saturated fats) on semen quality in male subjects. The study showed that the traditional Dutch diet increased sperm concentration. Opposite findings were reported by Danish investigators. Jensen et al.²³ on a sample of young Danish men from the general population, reported an association between the increased intake of saturated fat and a lower total sperm count and sperm concentration. It should be noted that the mechanism underlying the effects of saturated fatty acids on spermatogenesis and semen quality has not been elucidated.

Results of the present study have not demonstrated any association between the intake of vitamins: A, β -carotene, D, C, E, B₁, B₂, B₃, B₆, B₁₂, folic acid and the semen parameters examined. Other studies also showed no association between the intake of vitamins B₆, B₁₂, D, E, folic acid and semen quality (semen volume, sperm concentration, total sperm count, sperm motility, progressive sperm motility, total progressively motile sperm).^{7,8} There are, however, reports that suggest the presence of an association between the intake of antioxidant vitamins and semen parameters (semen volume, total sperm count,

sperm motility, sperm concentration, progressive sperm motility). Mínguez-Alarcano et al.⁸ suggest a positive association between the dietary intake of vitamin C, β -carotene and total motile sperm count in young healthy males. The semen volume increased with higher intake of these antioxidants. Similarly, Eskenazi et al.⁷ reported that men with higher intake of β -carotene had better sperm concentrations and progressive sperm motility than men with low intake. The present study did not demonstrate an association between the intake of antioxidants and the semen parameters examined, which could have been caused by the fact that the subjects consumed small amounts of fresh fruits and vegetables (<500 g/day).

The literature lacks convincing and unequivocal information on the relationship between caffeine consumption and semen quality. Some studies have reported that caffeine may be associated with high levels of testosterone and sex hormone-binding globulin and low levels of estrogen, but no effect on semen quality has been found.^{24,25} Swan et al.²⁶ claimed that a high cola (>14 0.5-litre bottles/week) and/or caffeine (>800 mg/day) intake was associated with a reduced sperm concentration and a lower total sperm count, although this was only significant for cola intake. Jensen et al.²³ showed that caffeine intake of <800 mg per day (about 7 cups of coffee) was not associated with reduced semen quality. However, men with a high caffeine intake had a slight reduction in semen quality, but it was not statistically significant and they had less healthy diet (they ate more fatty food, drank more alcohol and smoked more often). The present study also showed no association between the consumption of caffeine (originating from coffee, tea and soft drinks) and the semen parameters examined. The subjects consumed caffeine in the amount of about 96 mg per day (about 2 cups of coffee).

Potential limitations of the study include reliability and validity of the estimation of the average food intakes which were based on subjective assessments by the subjects. The region of Poland from which the volunteers originated is inhabited by a population of the same genetic background (nearly 100% are Caucasian). We are aware of the fact that our results pertain best to men with a higher level of education, from urban areas and without specific exposures to

chemicals or toxins. The subjects who decided to participate in the study might have been interested in their health status more than the average man.

CONCLUSION

The number of the selected dietary ingredients may significantly affect the semen quality of the male population of the Lower Silesia region of Poland. The study showed a favourable association between the intake of saturated, monounsaturated fatty acids and immotility and energy derived from fat and immotility and rapid (a) and slow (b) progressive motility. An unfavourable association was also shown between the energy value of the diet and sperm concentration, energy derived from the consumption of carbohydrates and semen volume, consistency and the energy derived from the consumption of fat and sperm consistency and immotility. Further research is needed to confirm these findings and extend these results to other populations.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

FUNDING SOURCES

Departmental sources of the University School of Physical Education, Wrocław, Poland.

REFERENCES

1. Esmaeili V, Shahverdi AH, Moghadasian MH, et al. Dietary fatty acids affect semen quality: a review. *Andrology* 2015;3(3):450–61.
2. Gaskins AJ, Colaci DS, Mendiola J, et al. Dietary patterns and semen quality in young men. *Hum Reprod* 2012;27(10):2899–907.
3. Attaman JA, Toth TL, Furtado J, et al. Dietary fat and semen quality among men attending a fertility clinic. *Hum Reprod* 2012;27(5):1466–74.
4. Chavarro JE, Toth TL, Sadio SM, et al. Soy food and isoflavone intake in relation to semen quality parameters among men from an infertility clinic. *Hum Reprod* 2008;23(11):2584–90.
5. Vujkovic M, de Vries JH, Dohle GR, et al. Associations between dietary patterns and semen quality in men undergoing IVF/ICSI treatment. *Hum Reprod* 2009;24(6):1304–12.

6. Cutillas-Tolín A, Mínguez-Alarcón L, Mendiola J, et al. Mediterranean and western dietary patterns are related to markers of testicular function among healthy men. *Hum Reprod* 2015;30(12):2945–55.
7. Eskenazi B, Kidd SA, Marks AR, et al. Antioxidant intake is associated with semen quality in healthy men. *Hum Reprod* 2005;20:1006–12.
8. Mínguez-Alarcón L, Mendiola J, López-Espín JJ, et al. Dietary intake of antioxidant nutrients is associated with semen quality in young university students. *Hum Reprod* 2012;27(9):2807–14.
9. Zareba P, Colaci DS, Afeiche M, et al. Semen quality in relation to antioxidant intake in a healthy male population. *Fertil Steril* 2013;100(6):1572–79.
10. Liu CY, Chou YC, Chao JC, et al. Association between dietary patterns and semen quality in a general Asian population of 7282 males. *PLoS One* 2015;10(7):e0134224.
11. Eslamian G, Amirjannati N, Rashidkhani B, et al. Adherence to the Western Pattern is potentially an unfavorable indicator of asthenozoospermia risk: a case-control study. *J Am Coll Nutr* 2016;35(1):50–8.
12. Karayiannis D, Kontogianni MD, Mendorou C, et al. Association between adherence to the Mediterranean diet and semen quality parameters in male partners of couples attempting fertility. *Hum Reprod* 2017;32(1):215–22.
13. Kunachowicz H, Nadolna I, Przygoda B, Iwanow K. Tables of nutritional value of food products and dishes. 3rd edition extended and updated. National Food and Nutrition Institute, Warsaw; 2005. Available at: <http://www.izz.waw.pl/en/usugi/13-o-nas/450-dieta-5>.
14. WHO. WHO laboratory manual for the examination and processing of human semen. Fifth Edition ed. Geneva: Author; 2010.
15. Afeiche MC, Williams PL, Mendiola J, et al. Dairy food intake in relation to semen quality and reproductive hormone levels among physically active young men. *Hum Reprod* 2013;28(8):2265–75.
16. Belloc S, Cohen-Bacrie M, Amar E, et al. High body mass index has a deleterious effect on semen parameters except morphology: results from a large cohort study. *Fertil Steril* 2014;102(5):1268–73.
17. Tsoo CW, Liu CY, Chou YC, et al. Exploration of the association between obesity and semen quality in a 7630 male population. *PLoS One* 2015;10(3):e0119458.
18. Eslamian G, Amirjannati N, Rashidkhani B, et al. Nutrient patterns and asthenozoospermia: a case-control study. *Andrologia* 2017;49(3).
19. Mendiola J, Torres-Cantero AM, Moreno-Grau JM, et al. Food intake and its relationship with semen quality: a case-control study. *Fertil Steril* 2009;91(3):812–18.
20. Attaman JA, Toth TL, Furtado J, et al. Dietary fat and semen quality among men attending a fertility clinic. *Hum Reprod* 2012;27(5):1466–74.
21. Alizadeh A, Esmaeili V, Shahverdi A, Rashidi L. Dietary fish oil can change sperm parameters and fatty acid profiles of ram sperm during oil consumption period and after removal of oil source. *Cell J* 2014;16(3):289–98.
22. Chavarro JE, Mínguez-Alarcón L, Mendiola J, et al. Trans fatty acid intake is inversely related to total sperm count in young healthy men. *Hum Reprod* 2014;29(3):423–40.
23. Jensen TK, Heitmann BL, Blomberg Jensen M, et al. High dietary intake of saturated fat is associated with reduced semen quality among 701 young Danish men from the general population. *Am J Clin Nutr* 2013;97(2):411–18.
24. Younglai EV, Holloway AC, Foster WG. Environmental and occupational factors affecting fertility and IVF success. *Hum Reprod Update* 2005;11(1):43–57.
25. Ramlau-Hansen CH, Thulstrup AM, Bonde JP, et al. Semen quality according to prenatal coffee and present caffeine exposure: two decades of follow-up of a pregnancy cohort. *Hum Reprod* 2008;23(12):2799–805.
26. Swan SH, Brazil C, Drobnis EZ, et al. and Study For Future Families Research Group. Geographic differences in semen quality of fertile U.S. males. *Environ Health Perspect* 2003;111(4):414–20.