Food supplements consumption and the role of pharmacies: a north-eastern Italy observational study

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Abstract

Background & Aims. The inappropriate use of food supplements can potentially cause harms to patients. The role played by pharmacists in advising citizens and purchasing these products, can contribute in improving their safer use but the knowledge, attitudes and practice of these professionals on this topic is still largely unknown.

Methods. Pharmacists of the Italian Region of Friuli-Venezia Giulia (FVG) were surveyed through a 47-items online questionnaire from Sept 2020 to Feb 2021. Questions investigated on knowledge (20 items), attitudes and practice (27 items). Data about sex, age, years of experience, degree, role within pharmacy (owner, employee) were also collected.

Results. 232 questionnaires were collected, most of which (71%) from women. The majority of responders had a Pharmacy degree (77%) and were employees within pharmacies (66%) where they have been working for at least 10 years (61%). Pharmacists' knowledge resulted to be poor with less than half participants scoring above the median value of 11; knowledge was higher among more experienced pharmacists. Larger gaps identified included the possible carcinogenicity of multivitamin's abuse and the undesired presence of non-labeled components in food supplements. Responders with less working experience felt more unprepared about vitamin's dosage and groups of patients with particular diseases ($p<0.05$). Employees reported the attitude of purchasing food supplements under patient direct request more frequently than owners ($p<0.05$).

Conclusions. Pharmacists' knowledge level on food supplements is unsatisfactory, and the effect of this lack on patient safety is concerning. Young professionals in particular would benefit further education the most on this specific public health topic.

Background

Food supplement, as defined by the Food and Drug Administration (FDA), is a product intended to supplement the diet by increasing the total daily intake, or an extract, metabolite, concentrate, constituent or combination of at least one of the following dietary ingredients: vitamins, minerals, herbs or other botanicals, amino acids. [1] In some peculiar clinical conditions, such as oncological or hematological diseases, the use of food supplements can take on great importance in supporting patients with alterations in the state of nutrition, particularly by defect. [2] [3]

At European level, the use of vitamins and minerals in supplements and their addition to food is regulated by the most recent European Community (EC) text 1170/2009 of 30th November 2009, which amends EC Directive 2002/46/EC and Regulation 1925/2006. According to the Italian Ministry of Health, vitamin supplements should not be used as food substitutes, whilst as a diet supplement with the aim of nutritional intake optimization, substances of nutritional interest with a protective or trophic effect provision or metabolism and physiological functions of the organism improvement". [4]

The list of substances and plant preparations allowed for use in food supplements, as well as the indications on the requirements to be respected for the safety and protection of consumers, are reported in the Italian Decree of 10th August 2018 entitled "Discipline for use in food supplements of and herbal preparations "and its subsequent amendments (Italian Ministerial Decree of 09/01/2019). Food supplements are usually available in pre-dosed forms such as capsules, tablets, liquids contained in ampoules or bottles with droppers.

Currently, the food supplement industry is one of the fastest growing: in 2018 there were 32 million Italians who consumed food supplements, the majority of whom were adult (approximately 63%) and female (60%). This sales volume in 2018 produced a growth in the market value of 3.3 billion (+126%) and in employment in the sector, which grew by 44% in 3 years. [5] Among the factors that have contributed to this growth in consumption are the growing ageing of the population, greater awareness of the cause-effect relationship between disease and diet as well as the importance of preventive health practices for the protection of health individual. [6] [7] For these reasons, consumers probably increasingly rely on food supplements to achieve the recommended daily amount of vitamins and trace elements in their diet, sometimes attaching little importance to their intake through food. [8]

However, the inappropriate use of supplements can potentially cause adverse effects, such as for example an increased risk of bleeding from vitamin E overdose, the onset of ataxia, alopecia, hepatotoxicity and teratogenicity from chronic vitamin A overdose; moreover, important drug interactions can arise with certain drug classes such as between vitamin K and oral anticoagulants. [9] [10] [2] According to EC Regulation 852/2004, food supplements can only be marketed by food business operators. In Italy, the purchase of food supplements is free at pharmacies and specifically authorized commercial establishments, the so-called para-pharmacies, in accomplishment with 32nd article of the decree no. 201 of 6th December 2011, and its subsequent amendments (law no. 214 of 22nd December 2011). [4] [11]

Being pharmacies one of the main places to buy food supplements, [4] pharmacists play a key role in advising citizens on the purchase and use of these products, as reported by the Italian Centre for Social Studies and Policies (CENSIS) [4] and QuintilesIMS (IQVIA) 2019 data; [12] indeed, 82% of Italians received advice for food supplements buying either from a doctor or a pharmacist [4] and 95% of the supplement food market is developed in pharmacies (86%) and para-pharmacies (9%). [12] [13] However, as revealed by a survey conducted on Italian pharmacists in 2016, the 26.4% of the interviewees report a lack of information regarding the choice of the most appropriate product for the user, on possible side effects or interactions with other products. [12] In addition, consumer confidence in the pharmacist as an adequate professional figure to provide advice on the use of supplements is not always adequate. [14] [15] In this regard, in 2018 the Scientific Association of Italian Pharmacists (ASFI) proposed that food supplements with health purposes and nutraceuticals become the subject of more stringent legislation to prevent possible abuses and at the same time limit the current confusion and disorientation of both pharmacists and citizens. [16]

Considering pharmacies a strategic and central hub for many aspects of the population health, with the regional law no. 70 of 5th December 2019, the Italian Friuli-Venezia Giulia (FVG) Region has given pharmacies the role of health points, [17] and therefore food supplement counselling could be one of the main

topic to be improved. This study aims to evaluate knowledge, attitudes and professional experiences of pharmacists operating in FVG Region concerning food supplements. [18]

Material And Methods

Study design

A cross-sectional observational study was conducted aiming at evaluating knowledge, attitudes and professional experiences regarding food supplements of pharmacists operating within both public and private authorized pharmacies of FVG Region. Homoeopathic or phytotherapeutic agents were not included in the survey by study design.

The 54-items online survey was developed by a multi-disciplinary group including public health professionals, pharmacists and a clinical pharmacologist. The survey was developed after consultation of available scientific literature; [5] [7] amendments on specific items were made considering the Italian regulatory context concerning the sale of food supplements.

The survey included two sections (1) KAP - knowledge, attitudes, practices - section with a total of 47 items, and (2) sociodemographic section, with seven multiple-choice questions, see Tables 1.1, 1.2 and 1.3. Questions 1.1 to 1.20 were true/false/not known questions aimed at evaluating knowledge, while questions 2.1.1 to 2.23 asked to express agreement/disagreement on a 5-point Likert scale (1-strongly disagree, 5-strongly agree) on attitudes, opinions and behaviors. Collected sociodemographic information included age, sex, educational background, years of professional experience, public vs private pharmacies as workplace, role within pharmacy (owner or employee).

Data collection

The survey was available online from September 2020 to February 2021. With the collaboration of the four professional associations of pharmacists of Gorizia, Pordenone, Trieste and Udine provinces of FVG Region and the support of the regional Office of the Italian Pharmacies Federation (Federfarma), participation to the survey was proposed via e-mail to all 1,600 pharmacists of FVG Region. Pharmacists were introduced the survey, the rationale of the study and its targets, and they were given the survey link. Reminders were sent to encourage participation during data collection period. Pharmacists working within hospital pharmacies were not included in the study, as their role in food supplement counselling to patients was considered too specific to inpatients to be compared with those directed to citizens. The anonymous online survey was developed by using the European platform EUSurvey; participation was completely free and without any refund. Participants, after reading all information, gave consent to their participation and proceeded with the compilation. Data were collected and managed in compliance with the European General Data Protection Regulation Privacy (EU-GDPR n. 2016/679). Estimating the frequency of good knowledge on food supplements among target population in 50%, considering a confidence level of 90% and that the adherence rate to online surveys is estimated to be around 20% [19], a sample size of 232 participants was calculated. The study protocol was approved by the Institutional Review Board of the University of Udine, Italy.

Data analysis

Descriptive analyses were carried out by calculating absolute numbers and relative frequency distributions for categorical variables as well as median, mean, and standard deviation (SD) for the numerical variables normally distributed. Statistical analyses were performed using used Chi-square test, Shapiro-Wilk for normality and Mann Whitney as non-parametric test. A p-value<0,05 was considered statistically significant.

Results

We collected 232 surveys, 164 (70.7%) from females and 68 (29.3%) from males; 179 responders (77.2%) had a degree in Pharmacy, while the remaining 53 (22.8%) in Chemistry and Pharmaceutical Tech. The majority (142; 61.2%) had more than 10 years of work experience, 39 (16.8%) form 6 to 10 years, 44 (19.0%) 1-5 years and only 7 (3.0%) less than 1 year. Almost all (188, 81.0%) worked in a private pharmacy and the majority (152, 65.5%) of responders were employees, while the other 80 (34.5%) were owner of the activities.

Knowledge

On the other hand, evaluating answers given by each participant, we obtained that the median value for correct answers was 11 out of 20 (QI 25-75: 10; 14). Considering, for this reason, more than 11 correct answers as the minimum standard, we noticed that the only characteristic that had a statistically significant impact on knowledge was the work experience: 30 responders out of 90 (33.3%) having 10 or less years of experience reached the minimum standard, while for those with 11 or more years of work experience the proportion of questionnaires with more than 11 correct answers was 55.6% (79/142).

Attitudes and practices

Table 3 summarizes the median Likert values for each question stratified for the main responders' characteristics and for the minimum standard of knowledge (12 correct answers). Analyzing the impact of characteristics on the median value between groups, we obtained that the statistically significant differences were more present for "number of correct answers " with 9 items that were evaluated in different way; it was followed by "type of degree" (8 items), "years of experience" and "role" (both 7) and "gender" (only 4 items out of 31). Questions that had generated the more heterogeneity in the answers between groups were the 2.4, 2.21.1 (different in groups for 4 characteristics) and 2.1.1 and 2.3 (different in groups for 3 characteristics).

Discussion

To the best of our knowledge, this is the first study exploring knowledge, attitudes, and professional practice regarding vitamin supplements of pharmacists in Friuli-Venezia Giulia Region. Generally, this study showed that pharmacists' knowledge about vitamin supplements is scarce, even if work experience showed to have a significant impact for a better knowledge level. Diet and nutrition play a key role in the maintenance of well-being and for non-communicable disease prevention and while a well-balanced diet aims at providing the essential nutrients, the role of dietary supplements in complementing the diet cannot be ruled out. Dietary supplement represent an important source of essential nutrients and may confer various health benefits, including chronic disease prevention. [20] However, wide usage of these supplements is often cause of concern because of their potential adverse effects as neurologic disturbances, gastrointestinal symptoms, hepatotoxicity, birth defects and drug interactions [21]. Pharmacists participating in our study seems to be strongly aware of the role of a varied diet in providing an adequate vitamin intake (94%) and also that some lifestyles (97%) and the chronic use of some drugs can cause a significant deficit of vitamins (97%). Conversely, lesser-known aspects, particularly among pharmacists with less than 10 years of experience, are the existence of a possible link between cancer and multivitamin's abuse, [22] [23] [24] [25] [26] the adverse effects of an excessive vitamin intake and the appropriate daily dosage of vitamin supplements. [27] [28] [29] Pharmacists' knowledge is also lacking regarding the presence of non-labeled agents in vitamin supplements (11%), [30] and the appropriate daily dosage of food supplements, particularly in the same subgroup. The use of food supplements and counselling in particular group of patients, e.g. those with oncological disease, is little known, probably because the management of these patients still takes place for the major part within acute-care hospitals.

Regarding professional practice and attitudes, pharmacists are confident with their responsibility in counselling patients as they believe their role being central and that the pharmacy setting being the safest places to sell vitamin supplements. This belief reflects the Italian reality as actually the 92% of vitamin supplement are sold by pharmacies, [12] generating nearly 10.6% of their income. Differences emerged also regarding some ethical issues, in particular with employees more frequently reporting the attitude to purchase food supplements under patient request.

Nevertheless, pharmacists report to be very careful in checking medical and pharmacological history of patients, paying attention to possible interactions and adverse effects due to simultaneous intake of drugs and food supplements. Awareness of the fundamental role of a healthy lifestyle and about natural sources of vitamins seems quite high. Finally, the urgent need of a continuous process of education and update is strongly supported by these results and also already reported by Italian pharmacists in a survey conducted in 2016 showing that 26.4% of them denouncing a lack of knowledge about side effects, interactions and quality of vitamin supplements sold to consumers. [12] Therefore it will be important to sustain a shared continuous education, in particular aimed to avoid different approaches emerged from the attitudes and practices results and among roles within pharmacy.

Conclusion

Pharmacists' knowledge about food supplements is scarce and young professionals in particular need further education to ensure a safe and effective purchase of these products to patients. Attitudes are generally good and consider patient's medical and pharmacological history while the counselling cover every aspect of food supplement consumption, from dosage to possible adverse effect

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests

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Authors' contribution statement:

LB, LA, LC, PC designed the research; Md'A and GM collected data; GM, Md'A, LB, LA discussed investigation methodology and contributed to result interpretation; LA performed data analysis; LB, LA supervised the study conduction; Md'A, GM, LB wrote the original draft; MP revised contents; all authors revised the paper and agreed with the final version of the manuscript.

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Not applicable

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Tables

Table 1. English version of the survey administered to FVG pharmacists.

Question code	Text of the question
Section 1: Knowledge	
(true/false question)	
1.1	A balanced provision of nutrients is guaranteed by the adoption of a varied diet rather than by using multivitamin supplements
1.2	Multivitamin supplements may contain non-labeled toxic ingredients
1.3	Increasing evidence supports the hypothesis that some types of cancer are caused by the abuse of multivitamins (commonly used as antioxidants)
1.4	Some lifestyles can reduce the absorption of vitamins or cause their complete depletion
1.5	The chronic use of some drugs can cause a significant deficit of vitamins
1.6	Important drug interactions and side effects can be enhanced by the concomitant intake of vitamin supplements
1.7	The recommended daily allowance (RDA) of vitamin C for an adult woman (19-50 years old) is 70 mg
1.8	The recommended daily dose of vitamin K is 90 µg
1.9	Excessive intake of Vitamin D (higher than the RDA) can cause loss of appetite, vomiting and increased urination frequency
1.10	The recommended daily allowance (RDA) for folic acid in a man adult is 400 µg
1.11	The recommended daily allowance (RDA) in men and women between 51 and 70 years for Vitamin D is 400 IU
1.12	Excessive intake of Vitamin E can increase the risk of hemorrhagic stroke, development of skin hematomas, bleeding and headache
1.13	The presence of cracks in the corners of the mouth may indicate a deficit of Vitamin B12
1.14	The presence of dandruff may indicate a Biotin deficiency
1.15	Conjunctival dryness can indicate a Vitamin A deficiency
1.16	Poor ability to concentrate can indicate a Vitamin B12 deficiency
1.17	The intake of high doses of antioxidant vitamins (A, C, E) can interfere with the effectiveness of some chemotherapy drugs
1.18	The administration of branched-chain amino acids and acid eicosapantenoic (EPA) can help reducing loss of weight and muscle mass in cancer patients
1.19	Beta-hydroxy-beta-methylbutyrate (HMB) is an active metabolite of leucine which could help reduce muscle loss, which is frequently observed in oncological disease
1.20	Pharmacists can dispense all vitamin supplements without prescription
Section 2: Attitudes, practices	
(Likert scale: strongly agree/agree/neither agree or disagree/disagree/strongly disagree)	
2.1	Providing information about vitamins to patients and citizens is part of the pharmacists' professional responsibility because:
2.1.1	pharmacists are professionals specifically trained for this aim
2.1.2	vitamins are not always over the counter (OTC) drugs
2.1.3	there is a lack of other trained professionals on this topic
2.2	Before recommending a food supplement, the medical history of the single consumer should be investigated to exclude any contraindications upon hiring
2.3	I have enough information about the recommendations for the use of vitamins supplements in specific population target groups
2.4	Pharmacists play a fundamental role in supporting an appropriate nutrition in oncologic patients, by providing oral nutritional supplements, modular supplements and nutraceuticals
2.5	It happens to receive pressures from manufacturers of food supplements to increase their sale
2.6	Each consumer should always be counselled about natural sources of vitamins intake
2.7	Pharmacists should provide updated information and dedicated seminars to other healthcare professionals
2.8	I have enough information about adverse effects of vitamins if assumed at dosages higher than recommended
2.9	Pharmacists should be responsible for security only regarding vitamins supplements dispensed in their pharmacy
2.10	Consumers should be individually counseled about dosage and via of administration of food supplements
2.11	Vitamin supplement products should be sold only in pharmacy settings
2.11.1	because they are drug
2.11.2	because it is safer for patients

2.11.3	to have more control on pricing and cost
2.12	I am informed enough regarding their contraindications in specific groups of patients (i.e diabetics, epileptics, having anticoagulant therapy).
2.13	I recommend food supplements to all consumers, being confident of their safety and effectiveness
2.14	I have enough knowledge about dosage and administration of vitamins as dietetic supplements
2.15	It is recommended to update periodically about scientific evidence concerning vitamin supplements on paper supports or official/institutional websites
2.16	The choice of food supplement should be dictated by both economic and effectiveness evaluations
2.17	I have enough knowledge about interactions between drugs and food supplements
2.18	It is necessary to report any adverse effects (related upon the hiring of food supplement and reported from the patient) to the qualified Health Authority
2.19	I believe that pharmacists are often induced to encourage the consumption of vitamin supplements
2.20	It is necessary to inform the single consumer about possible adverse effects of the vitamin supplements
2.21	As a pharmacist, I recommend consumers about a healthy lifestyle and food supplements consumption, particularly:
2.21.1	checking the vitamin intake with food to avoid overdose from contemporary hiring of vitamin supplements
2.21.2	recommending appropriate way of storage and cooking of fruits and vegetables
2.21.3	recommending an adequate daily water intake
2.21.4	banning on alcohol consumption
2.21.5	banning on smoke habit
2.22	I often sell vitamin supplements because of a specific request of a patient, even if supplementation is not necessary
2.23	It is necessary to check if a particular food supplement interacts with any medications hired form the single patient

Section 3: Sociodemographic information

(multiple choice questions)

Sex	Male	Female				
Age (years)						
Degree	Pharmacy		Chemistry and Pharmaceutical Technologies			
Further training: (multiple choice)	Master in Food Sciences		Specialization in Food Sciences		Other courses	None
Years of professional experience	< 1	1-5	6-10	11-15	16-20	> 20
Pharmacy type	Public	Private				
Role	Owner	Employee				

Table 2.

		Gender			Type of degree			Years of experience			Role		
Question code	Overall knowledge (%)	Female n. 164	Male n. 68		.Pharmacy n. 179	Chem. and Pharm. Tech n. 53		10 or less n. 90	11 or more n. 142		Employee n. 152	Owner n. 80	
		% of correct answers		p	% of correct answers		p	% of correct answers		p	% of correct answers		p
1.1	94.0	92.1	98.5		93.3	96.2		96.7	92.3		95.4	91.3	
1.2	11.2	10.4	13.2		11.7	9.40		7.80	13.4		10.5	12.5	
1.3	21.1	21.3	20.6		24.0	11.3		18.9	22.5		21.7	20.0	
1.4	97.0	97.6	95.6		97.2	96.2		97.8	96.5		96.7	97.5	
1.5	97.4	97.6	97.1		97.2	98.1		97.8	97.2		97.4	97.5	
1.6	85.8	86.6	83.8		87.7	79.2		84.4	86.6		82.9	91.3	
1.7	45.3	42.7	51.5		46.9	39.6		34.4	52.1	<0.05	39.5	56.3	<0.05
1.8	20.7	21.3	19.1		20.7	20.8		15.6	23.9		19.7	22.5	
1.9	50.0	53.0	42.6		50.3	49.1		51.1	49.3		50.7	48.8	
1.10	51.3	52.4	48.5		52.0	49.1		44.4	55.6		48.7	56.3	
1.11	60.3	57.3	67.6		61.5	56.6		50.0	66.9	<0.05	55.9	68.8	
1.12	32.3	31.1	35.3		32.4	32.1		26.7	35.9		31.6	33.8	
1.13	75.0	80.5	61.8	<0.05	74.9	75.5		86.7	67.6	<0.05	80.9	63.8	<0.05
1.14	62.5	61.6	64.7		62.6	62.3		63.3	62.0		62.5	62.5	
1.15	67.2	68.3	64.7		67.6	66.0		67.8	66.9		65.1	71.3	
1.16	79.3	82.3	72.1		78.8	81.1		81.1	78.2		82.9	72.5	
1.17	62.9	63.4	61.8		63.1	62.3		58.9	65.5		62.5	63.8	
1.18	41.8	40.2	45.6		41.3	43.4		31.1	48.6	<0.05	38.8	47.5	
1.19	34.9	34.1	36.8		33.5	39.6		34.4	35.2		34.9	35.0	
1.20	76.7	77.4	75.0		74.9	83.0		75.6	77.5		75.7	78.8	

Table 3.

		Sex			Type of degree			Years of experience			Role			Number of co answers	
Question code	Median value	Female n. 164	Male n. 68		.Pharmacy n. 179	Chem. and Pharm. Tech n. 53		10 or less n. 90	11 or more n. 142		Employee n. 152	Owner n. 80		11 or less n. 118	more than 11 n. 114
		Median value		p	Median value		p	Median value		p	Median value		p	Median value	
2.1.1	4.04	4.00	4.15		4.13	3.74	<0.05	3.89	4.14	<0.05	3.97	4.19	<0.05	3.93	4.16
2.1.2	4.39	4.34	4.50		4.42	4.28		4.33	4.42		4.39	4.37		4.28	4.50
2.1.3	3.34	3.41	3.15		3.24	3.66	<0.05	3.34	3.33		3.44	3.14		3.43	3.24
2.2	4.75	4.78	4.66		4.78	4.64		4.76	4.74		4.70	4.84	<0.05	4.70	4.79
2.3	3.34	3.35	3.34		3.37	3.26		3.16	3.46	<0.05	3.24	3.55	<0.05	3.02	3.68
2.4	3.44	3.30	3.76	<0.05	3.51	3.19		3.04	3.69	<0.05	3.28	3.74	<0.05	3.25	3.64
2.5	2.23	2.15	2.44		2.24	2.21		2.27	2.21		2.28	2.14		2.26	2.20
2.6	4.72	4.72	4.72		4.73	4.68		4.00	4.76		4.72	4.73		4.71	4.73
2.7	3.87	3.91	3.79		3.91	3.75		4.66	3.88		3.8	4.01		3.69	4.07
2.8	3.20	3.16	3.29		3.29	2.89	<0.05	3.87	3.25		3.16	3.26		2.95	3.46
2.9	2.84	2.79	2.94		2.87	2.72		3.11	2.87		2.83	2.85		2.94	2.73
2.10	4.87	4.87	4.87		4.88	4.81	<0.05	2.79	4.88		4.85	4.90		4.81	4.92
2.11.1	3.64	3.60	3.74		3.7	3.45		4.84	3.63		3.59	3.75		3.62	3.67
2.11.2	4.54	4.59	4.43		4.51	4.62		3.67	4.54		4.53	4.56		4.49	4.59
2.11.3	2.92	2.95	2.85		2.93	2.87		4.54	2.84		2.96	2.84		3.01	2.82
2.12	3.17	3.12	3.29		3.25	2.92		3.04	3.23		3.10	3.31		2.94	3.41
2.13	2.56	2.52	2.66		2.53	2.66		2.44	2.63		2.43	2.81	<0.05	2.62	2.50
2.14	3.34	3.26	3.51		3.42	3.06	<0.05	3.16	3.45	<0.05	3.24	3.53		3.23	3.45
2.15	4.82	4.83	4.81		4.85	4.72	<0.05	4.88	4.79		4.82	4.83		4.82	4.82
2.16	3.55	3.46	3.76		3.53	3.62		3.49	3.58		3.51	3.61		3.59	3.50
2.17	3.30	3.30	3.29		3.35	3.13		3.23	3.35		3.26	3.37		3.04	3.57
2.18	4.70	4.79	4.49	<0.05	4.72	4.66		4.73	4.68		4.76	4.59		4.64	4.76
2.19	2.85	2.75	3.10		2.74	3.25	<0.05	3.00	2.76		2.99	2.59	<0.05	2.88	2.82
2.20	4.76	4.76	4.76		4.79	4.64		4.71	4.79		4.72	4.82		4.75	4.77
2.21.1	4.37	4.29	4.56	<0.05	4.46	4.08	<0.05	4.20	4.48	<0.05	4.33	4.45		4.20	4.54
2.21.2	4.42	4.43	4.40		4.45	4.34		4.33	4.48		4.38	4.51		4.32	4.53
2.21.3	4.80	4.82	4.76		4.83	4.70		4.73	4.85	<0.05	4.78	4.84		4.77	4.83
2.21.4	4.58	4.66	4.38	<0.05	4.56	4.64		4.49	4.63		4.53	4.66		4.53	4.63
2.21.5	4.77	4.76	4.79		4.78	4.75		4.68	4.83	<0.05	4.75	4.81		4.73	4.82
2.22	3.35	3.34	3.40		3.31	3.51		3.46	3.29		3.56	2.96	<0.05	3.44	3.26
2.23	4.83	4.84	4.81		4.84	4.77		4.87	4.80		4.82	4.85		4.78	4.88