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Research Paper

Characteristics and associated morbidities of young adults with misconceived food allergy: A cross-sectional study

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ABSTRACT

Background: Many patients with self-reported food allergy are not allergic but suffer from similar burdens. We aimed to characterize young adults with misconceived food allergy.

Methods: A cross-sectional study of individuals (n = 12,592) aged 17–18 years, recruited to the Israel Defense Forces (IDF) at a single urban-area recruitment center over a six month-period. All participants underwent a comprehensive medical and psychological evaluation. Cognitive tests were performed and a Combined Intellectual-Education score assigned. Participants who reported food elimination due to allergy were skin-tested and underwent oral food challenges, when indicated. The characteristics, psychological evaluation and cognitive tests of individuals with no reported food allergy (n = 12,444), misconceived food allergy (n = 64) and true food allergy (n = 84) were compared.

Findings: The prevalence of atopic co-morbidities was higher in recruits reporting compared to those not reporting food allergy while the rate of other co-morbidities was comparable. Anxiety disorder was diagnosed significantly more in individuals who reported food allergy (4·1%) compared to those who did not (1·7%) (p = 0·04). Further analysis revealed that this diagnosis was concentrated in individuals with misconceived (8/64, 12·5%) compared to true food allergy (2/84, 2·4%), (p = 0·02). Patients with misconceived food allergy were mostly of female sex, had lower Combined Intellectual-Education scores compared to patients with true (p = 0·001) and no reported food allergy (p = 0·01), and required the longest mean evaluation time (147·6 ± 109·4 days).

Interpretation: Patients with misconceived food allergy have higher rates of anxiety disorder and are often from a lower educational level and of female sex. Medical and educational attention is required to improve care of this specific population.

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Introduction

IgE-mediated food allergy is an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food [1]. It is a major world-wide public health problem, estimated to effect up to 10% of specific populations [2]. Food-allergic patients are at risk of life-threatening reactions [1–3], with adolescents and young-adults being a particularly high-risk group [4]. Food-allergic patients need to be constantly vigilant about what they eat and to carry injectable epinephrine regularly. Beyond the atopic comorbidities [5–7] and potential nutritional deficiencies [8], food allergic patients suffer from a variety of age-related psychosocial problems, mainly anxiety and depression [9-12].

Most epidemiological studies on food allergy are based on patients' self-report only [13,14]. The few studies that based their diagnosis on objective criteria demonstrated that self-reported food allergy is inaccurate, and that many, and in some studies the majority, of the patients reporting food allergy are actually not allergic

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Research In Context

Evidence before this study

Many studies describe the wide difference between self-reported and true food allergy. However, none characterized patients who believed they were food allergic but were found not to be. We then searched Pubmed for all studies with the terms “food allergy”, "misconceived", or “mislabeled" published on or before November 2020 with no start date or language restrictions. Only 10 studies were found, and only a single study (published by our group) described infants with mislabeled cow's milk allergy. As far as we know, no study to date has characterized teenagers with misconceived food allergy.

Added value of this study

In this cross-sectional study including 12,592 recruits, we found that the 64 participants with misconceived food allergy were characterized by higher rates of anxiety disorder, a lower educational background, and by female sex.

Implications of all the available evidence

Separating patients with reported food allergy to those with true and those with a misconception of food allergy is imperative for the study of both groups. Better education and medical awareness of patients with misconceived food allergy might improve their diagnosis and care, and reduce the medical system burden.

[13–19]. For example, in a recent study nearly 19% of 40,443 adults who answered a telephone/internet interview believed that they have food allergy. However, after additional information was gathered from medical databases, food allergy was suspected in only 10·8% [17]. Additionally, in a recent multi-center European study, over 77% of 892 participants reporting food allergy were found to be non-allergic following a professional interview, sIgE testing and Oral Food Challenges (OFC) [15]. These individuals might unnecessarily adopt food allergy precautions and are prone to similar impairments in quality of life [3], psycho-social problems [9–12] and nutritional deficiencies [8] as true food-allergic patients. In addition, over diagnosis of food allergy affects all levels of food allergy care and significantly inflates the economic burden of this condition [20,21]. Currently, very little is known about patients who mistakenly believe they have food allergy. Importantly, it is not clear whether various characteristics attributed to patients with self-reported food allergy (i.e. psychosocial problems, such as anxiety and depression), reflect true food allergic patients or those with misconceived food allergy.

A military service is mandated in the overwhelming majority of Israeli youth (>18 years old). As young adults with various medical conditions are enlisted, all individuals undergo a thorough medical evaluation prior to their enlistment, at age seventeen. The main goal of this medical evaluation is to protect the future soldiers from serving in unsuitable conditions and to adjust the military service conditions to their health limits. During this evaluation process, recruits are required by law to arrive to any medical clinic deemed necessary for their evaluation process but they are not forced to undergo any test and do not suffer any sanctions in case they refuse. This comprehensive medical evaluation provides a unique opportunity for population-based studies in a westernized medical setting [22]. In a previous study, of 12,592 recruits included, 148 reported food avoidance due to allergy [22]. Of those, a little less than half were found to be non-allergic following evaluation including a detailed symptom-report and clinical history, skin prick tests (SPT) and oral food challenges (OFC). This group of well characterized individuals, undergoing an extensive medical, psychosocial and cognitive evaluation, provides a valuable platform to decipher the differences between individuals with misconceived food allergy, in comparison to true food allergic patients, and to those who did not report food allergy.

Methods

Participants

All individuals (17–18 years-old) who were in the process of drafting in a single urban area recruitment center of the Israel Defense Forces (IDF) located in the center of Israel, and who started their medical evaluation between May and October 2016 and completed it by October 2017 were eligible. This cohort is estimated to represent >90% of the Jewish non-ultra-orthodox population for this age in this region of the country [22,23]. The entire medical evaluation was performed as part of the routine drafting process in Israel. At the time the study was performed, there were no assignment limitations or special accommodations for food allergic soldiers and this information was available for the Israeli public. The IDF Institutional Review Board committee approval for collection and publication of data was obtained and patient informed consent for the retrospective data collection without patient identifiers was waived.

Medical information

Recruits were interviewed by the recruitment center physicians and completed a standardized comprehensive questionnaire inquiring about all potential diseases and medical conditions for this age group [22,24], the interview was followed by a physical examination. Additional information was obtained from primary care physician upon request. Medical diagnoses were translated into specific codes that were stored in a computerized database.

Mental health information

All recruits were interviewed by qualified personnel according to a screening questionnaire focused on potential psychiatric disorders. Recruits, suspected to have a psychiatric disorder were invited for a full psychiatric examination conducted by a certified psychiatrist. Psychiatric diseases and disorders were diagnosed according to the currently updated mental health assessing scales, based on the DSM (The diagnostic and statistical manual of mental disorders) 5 and ICD (The international classification of diseases) 10. Individuals diagnosed with psychosis or schizophrenia are exempted from military service, are not required to attend the recruitment center, and were therefore excluded.

Cognitive and intellectual-educational assessment

All recruits underwent a series of cognitive tests that were combined to produce a highly validated Cognitive Score, equivalent to a normally distributed Intellectual quotient (IQ) (see online supplementary text). In addition, a Combined Intellectual-Education score, comprised of the educational background, the cognitive tests and a personal interview is assigned to each recruit. This index is routinely used to examine each recruits' suitability for military service and also reflects his potential for advanced army positions.

Food allergy diagnosis

In a previous study, recruits were asked about deliberate elimination of a particular food for suspected allergy, as previously described [22]. All those who reported deliberate food elimination due to an allergy were referred to an allergist for further evaluation and skin

Table 1
Comparison of patients who did and did not report food allergy.

Category	Variable	No reported food allergy N = 12,444	Reported Food Allergy N = 148	p-value
Demographics	Sex, male	5716 (45·93%)	68 (45·95%)	1·0
	Height (cm)	168·15 (9·05) [168, 161−175]	167·7 (8·69) [167, 161−175]	0·64
	Weight (kg)	63·78 (14·39) [61, 54−71]	62·7 (13·34) [62, 53−70]	0·45
	BMI (kg/m^2)	22·47 (4·28) [21·6, 19·6−24·3]	22·24 (4·22) [21·5, 19·6−23·8]	0·41
Atopic co-morbidities	Chronic Rhinitis	833 (6·69%)	47 (31·76%)	<0·0001
	Atopic Dermatitis	210 (1·69%)	12 (8·11%)	<0·0001
	Asthma	740 (5·95%)	36 (24·3%)	<0·0001
Other co-morbidities	Urticaria, recurrent	61 (0·48%)	0 (0%)	1·0
	Celiac	261 (2·1%)	4 (2·7%)	0·56
	Rheumatic Diseases	121 (0·97%)	1 (0·68%)	1·0
	Diabetes Mellitus	50 (0·4%)	1 (0·68%)	0·45
	Hypothyroidism	113 (0·91%)	2 (1·35%)	0·39
Psychological co-morbidity	Anxiety Disorder	213 (1·71%)	6 (4·05%)	0·04
	Depression	85 (0·68%)	2 (1·35%)	0·27
Cognitive and educational assessment	Cognitive Score	56·8 (19·13) [60, 40−70]	57·9 (18·67) [60, 45−70]	0·48
	Combined Intellectual-Education Score	51·5 (3·35) [52,49−54]	51·64 (3·14) [52, 49−54]	0·76
Evaluation time (days)	37·8 ± 85·4	123·1 ± 99	<0·0001	

Categorical variables are presented with frequency (%) and continuous variables are presented with mean (SD) [median, IQR].

prick (SPT) and/or sIgE testing. In cases where the diagnosis of food allergy was questionable according to the study protocol (supplementary methods), recruits were referred to the Institute of Allergy, Immunology and Pediatric Pulmonology, at Shamir Medical Center, Zerifin, Israel for further evaluation. Recruits who met the criteria underwent OFCs (supplementary methods) [22] and a final status of true or misconceived food allergy was determined. Individuals with misconceived food allergy were further divided to groups according to the characteristics of their symptoms: Oral symptoms only (Group A), systemic reactions on initial consumption (Group B) or on consumption of a previously tolerated food (Group C), atypical symptoms (Group D), classical symptoms with undiagnosed recovery (Group E) or symptoms likely attributed to initial incorrect diagnosis (Group F).

Follow-up

Recruits were required to inform the recruitment center if any new medical information was revealed during the period between completion of the medical inquiry and the day of enlistment to the army. In addition, all new soldiers were asked about possible food allergy at least two more times (by army physicians during the first week of army service and prior to entrance to the dining area) months to years following their initial evaluation. Any new report of food allergy from the entire cohort and new medical information regarding the recruits reporting food allergy was transferred to the medical corps allergy unit.

Statistical analysis

Statistical analysis was performed using SAS 9·4 software. Univariate analyses included Chi-square test (or Fisher's exact test) for categorical variables, and t-test (or Wilcoxon two-sample test) for continuous variables. The study outcomes were the true food allergy and the misconceived food allergy (examined separately). Significant variables that were found in the univariate logistic regression analysis (specified in the results section) were included in the multivariable analysis. Stepwise logistic algorithm was implemented to establish the final model with all independent predictors. Adjusted odds ratios (Adj.OR) with 95% confidence interval (95%CI) are presented. Statistical significance was considered when $p < 0.05$.

Role of funding

The research reported in this publication was supported by the Israel Defense Forces (IDF) Medical Corps and Directorate of Defense Research & Development, Israeli Ministry of Defense (IMOD DDR&D). The funder was not involved in any aspect of the study.

Results

Overall, 12,592 recruits, aged seventeen years (46.5% males) were included in this study. Food avoidance due to an allergy was reported by 148 recruits and the diagnosis of food allergy was excluded in 64 (43·2% of them). The characteristics of individuals with and without reported food allergy, are detailed in Table 1.

Most excluded food allergies (n = 42, 65·6%) were to fruits, vegetables seeds, legumes and spices, which are not common regional allergenic foods (Table 2) [20]. For 10 recruits, allergies were excluded for more than a single food. Thirty-nine of the recruits with excluded food allergy (Table 2, Groups B + C) had acute symptoms that could reflect typical allergic reactions to the suspected foods (skin rash with or without angioedema, gastro-intestinal symptoms or acute dyspnea) but had not been evaluated by an allergist previously. Seven additional recruits (Group D) had symptoms that were unlikely a result of food allergy (atypical symptoms or too long interval from exposure). These recruits had no previous allergy evaluation as well. Thirteen recruits (Group A) reported symptoms that were limited to the oral cavity but only four of them underwent a formal allergy evaluation. All 13 were non-allergic at study entry. Six of these individuals had positive SPTs and might represent oral allergy syndrome. Three recruits (Group E) were diagnosed with milk/egg allergy in infancy but were not followed by an allergist since, and the timing of resolution of their allergy is not clear. Finally, two recruits (Group F) were diagnosed as food allergic by an allergist but review of their symptoms suggest that they were probably not allergic (one had symptoms suggestive of chronic spontaneous urticaria and the other experienced acute urticaria which was attributed to a fruit that was previously consumed regularly and uneventfully). Only 10 of the 64 recruits had evidence of sensitization (positive SPT) to the suspected foods during their current evaluation.

There were no significant differences in demographics between recruits who reported and those who did not report food allergy (Table 1). The prevalence of atopic co-morbidities: asthma, chronic rhinitis, [representing primarily allergic rhinitis in this age group [25] and atopic dermatitis, was significantly higher among recruits with reported food allergy (p<0·0001 to all). The prevalence of other co-morbidities, including auto-immune and rheumatic diseases, was comparable between the two groups (p > 0·39 to all). Anxiety disorder was significantly more prevalent among recruits reporting food allergy (p = 0·04), while the rate of depression was comparable

Table 2
Clinical characterization of patients' misconceived food allergy.

Group	Reasons for food elimination	Eliminated foods	Previous allergy evaluation	Current positive SPT
A (n = 13)	Oral symptoms only	Legumes (n = 1) Tree nuts+ peanuts (n = 4) Seeds (n = 2) Fish (n = 1) Fruits (n = 5)	4	6
B (n = 23)	Systemic symptoms on 1st exposure	Legumes (n = 1)Tree nuts+ peanuts (n = 3) Fruits (n = 14) Sesame (n = 2) Fish (n = 3)	0	2
C (n = 16)	Systemic symptoms to previously tolerated foods	Grain (n = 1)Tree nuts+ peanuts (n = 2) Egg (n = 2) Fruits (n = 6) Vegetables (n = 1) Spices (n = 4)	0	0
D (n = 7)	Atypical symptoms or too long time interval from food exposure	Grains (n = 1) Fish (n = 1) Fruits (n = 5)	0	0
E (n = 3)	Undiagnosed recovery	Milk (n = 2) Egg (n = 1)	3	1
F (n = 2)	Probable initial incorrect diagnosis	Tree nuts (n = 1) Fruit (n = 1)	2	1

Fruits - peach, kiwi, mango, apple, figs, strawberry, orange, pineapple, apricot, melon, watermelon, pomegranate, coconut; Vegetables- tomato, eggplant.
Legumes - soy, pea.
Seeds – pine, poppy.
Spices - cinnamon, others.
Grains- wheat.
Most recruits reported misconceived allergy to tree-nuts reported the same for peanuts and many patients reported misconceived allergy to more than a single fruit.

between the two groups (p = 0·27). Cognitive Scores and Combined Intellectual-Education scores were also comparable (p = 0·48 and p = 0·76 respectively) (Table 1). On multivariate analysis, only the rate of chronic rhinitis (Adj.OR 4·07 CI 2·66–6·23, p < 0·0001), atopic dermatitis (Adj.OR 2·56 CI 1·35–4·87, p = 0·04) and asthma (Adj.OR 2·4 95%CI 1·52–3·78, p = 0·0003) remained significantly different. The mean time required to complete the entire medical evaluation of recruits with reported food allergy was significantly longer than those without reported food allergy,123·1 ± 99 vs. 37·8 ± 85·4 days, respectively (p < 0·0001) (Table 1, Figure 1A).

Compared to recruits not reporting food allergy, true food allergic patients had more chronic rhinitis and asthma (p < 0·0001) and demonstrated higher Cognitive Scores (p = 0·02), (Table 3, Figure 2), while those with misconceived food allergy had female sex preponderance (p = 0·001), more chronic rhinitis (p < 0·0001), and atopic dermatitis (p = 0·02), and scored lower on Combined Intellectual-Education scores (p = 0·01) (Table 3, Figure 2) on multivariable analysis. The time required to complete the comprehensive medical evaluation in recruits with misconceived food allergy was significantly longer (147·6 ± 109·4 days) compared to recruits with true food allergy (104·5 ± 86·1 days) (p < 0·005), (Table 4, Figure 1B).

Recruits with true food allergy and those with misconceived food allergy were followed until their enlistment day (16·4, 12·6–19·6 median, IQR months) and their medical information was updated. During this follow-up period, four more cases of anxiety were diagnosed based on new accepted information and psychiatric evaluation, all in patients with misconceived food allergy. No other new medical diagnoses were made for patients reporting food allergies during this time period. More females were represented in the group with misconceived food allergy (Table 4), (p = 0·0001). Body Mass Index (BMI) was comparable between the two groups (p = 0·77), and so were height and weight after adjusting for sex (examined with gender stratification p > 0.84 for both genders). The rate of atopic dermatitis and chronic rhinitis was comparable in recruits with true and misconceived food allergy (p = 0·91 and p = 0·24 respectively) while asthma was more frequent in recruits with true food allergy (p = 0·004). The rate of non-atopic co-morbidities was comparable between the two groups. Recruits with true food allergy received

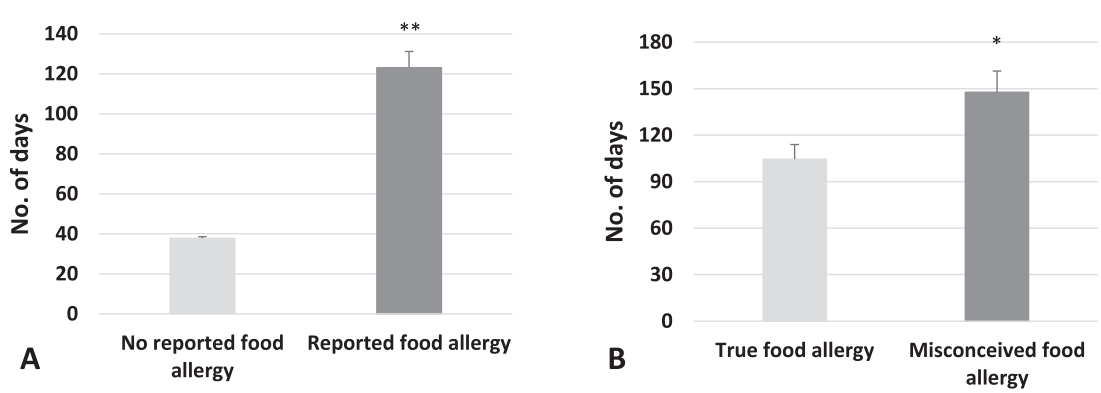

Fig. 1. Medical evaluation time in recruits with and without reported food allergy
The mean ± SEM (standard error of the mean) time (days) that was required for medical evaluation of recruits with and without reported food allergy (A) and in those with true and misconceived food allergy (B), is presented. Error bars represent SEM.
$^{*}p$ < 0•001, $^{**}p$ < 0•0001.

Table 3
Multivariate analysis for factors identifying individuals with true and misconceived food allergy compared to those with no reported food allergy (final model).

Category	Adj. OR	95% CI		*p*- value
		Lower limit	Upper limit	
True food allergy (*n* = 84) vs. no reported food allergy (*n* = 12,444)*				
Chronic rhinitis	4·58	2·66	7·9	<0·0001
Asthma	3·12	1·76	5·51	<0·0001
Cognitive Score‡	1·15	1·02	1·3	0·02
Misconceived food allergy (*n* = 64) vs. no reported food allergy (*n* = 12,444)**				
Gender - female	2·51	1·43	4·42	0·001
Chronic rhinitis	5·09	2·80	9·26	<0·0001
Atopic dermatitis	3·17	1·21	8·31	0·02
Combined Intellectual-Education Score	0·91	0·85	0·98	0·01

* On univariate analysis Gender, Height, Chronic rhinitis, Asthma, Cognitive Score and Combined Intellectual-Education Score were significant ($P<0·05$ to all) and they were considered in the multivariable logistic regression.

** On univariate analysis Gender, Height, Chronic rhinitis, Atopic Dermatitis, Anxiety, Cognitive Score and Combined Intellectual-Education Score were significant ($P<0·05$) and they were considered in the multivariable logistic regression
Adj.OR = adjusted odds ratio.

‡ For every 10 units increase.

higher Cognitive and Combined Intellectual-Education scores compared to those with misconceived food allergy (p = 0·0003 to both) (Table 4). In contrast, the rate of anxiety was significantly higher in recruits with misconceived food allergy (8, 12·5%) compared to true food allergic-patients (2, 2·4%), p = 0·002 (Fig. 3). On multivariable analysis, recruits with misconceived food allergy had female preponderance (Adj.OR 3·9, 95% CI 1·82–8·35, p = 0·0005), lower Combined Intellectual-Education scores (Adj.OR 0·83, 95% CI 0·73–0·93, p = 0·0018) and higher rate of anxiety disorders (Adj.OR 11·77, 95% CI 1·34–103·6) (the latter wide CI likely reflecting the overall small number of patients diagnosed with anxiety disorder), compared to recruits with true food allergy, c-statistic 76%, Hosmer and Lemeshow goodness of fit test p value = 0·5465

Of the 64 recruits with misconceived food allergy, 57 have entered army service during the 36 months following their medical evaluation. Four recruits were exempted from service due to the severity of their anxiety disorder and another three due to non-medical reasons. Despite the fact that food allergy was already excluded, 16 of the 57 recruits still reported food allergy during the first weeks of military service. Of those, four had been diagnosed with a psychiatric disorder. Additional allergy evaluations were performed in some of these recruits and reconfirmed they had no food allergy.

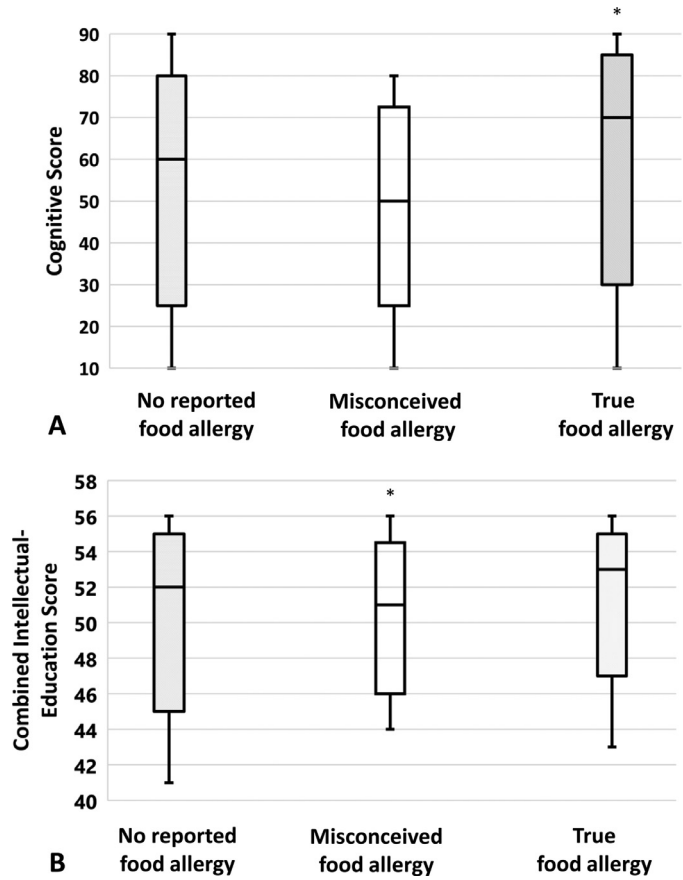

Fig. 2. The Cognitive Scores and the Combined Intellectual-Education scores of recruits with no reported food allergy, true and misconceived food allergy.

Box-plots of the median and IQR of the Cognitive Scores (A) and the Combined Intellectual-Education scores (B), compared between individuals who did not report food allergy, and those with true and misconceived food allergy, are presented. Whiskers represent medians, boxes represent IQR, and error bars represent range.

*$p < 0·005$.

Discussion

This large cohort study, based on a unique setting of mandatory military service together with an objective diagnosis of food allergy, demonstrates that a significant rate of individuals eliminate foods for

Table 4
Comparison of patients with true and misconceived food allergy.

Category	Variable	True food allergy *N* = 84	Misconceived food allergy *N* = 64	*p*-value
Demographics	Sex, male	50 (59·52%)	18 (28·13%)	0·0001
	Height (cm)	169·81 (8·15) [170, 162·6–177]	164·92 (8·67) [163,159–172]	0·006
	Weight (kg)	64·32 (13·11) [62·5, 55–71]	60·56 (13·43) [58, 50–67]	0·03
	BMI (kg/m^2)	22·28 (4·17) [21·6, 19·6–23·6]	22·19 (4·31) [20·7, 19·5–24·6]	0·77
Atopic co-morbidities	Chronic Rhinitis	30 (35·71%)	17 (26·56%)	0·24
	Atopic Dermatitis	7 (8·33%)	5 (7·81%)	0·91
	Asthma	26 (30·95%)	7 (10·93%)	0·004
Previous allergy evaluation	59 (70·2%)	9 (14·1%)	<0·0001	
Other co-morbidities	Urticaria, recurrent	0	0	–
	Celiac	1 (1·19%)	3 (4·69%)	0·32
	Rheumatic Diseases	1 (1·19%)	0	1·0
	Diabetes Mellitus	1 (1·19%)	0	1·0
	Hypothyroidism	0 (0%)	2 (3·13%)	0·19
Mental co-morbidity	Anxiety	2 (2·38%)	8 (12·5%)	0·002
	Depression	1 (1·19%)	1 (1·56%)	1·0
Psychosocial assessment	Cognitive Score	62·86 (17·39) [70, 50–80]	51·41 (18·42) [50,40–65]	0·0003
	Combined Intellectual-Education Score	52·45 (2·9) [53,51–54]	50·59 (3·16) [51,48–53]	0·0003
Evaluation time (days)	104·5 ± 86·1	147·6 ± 109·4	$p < 0·005$	

Categorical variables are presented with frequency (%) and continuous variables are presented with mean (SD) [median, IQR].

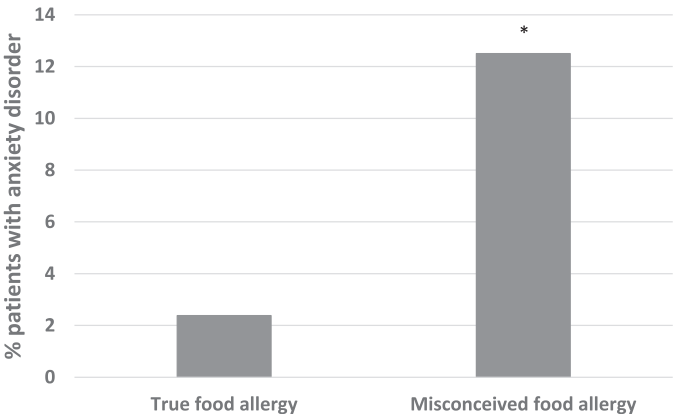

Fig. 3. The rate of anxiety disorder diagnosed in recruits with true and misconceived food allergy during army enlistment.

The percentage of recruits diagnosed with anxiety among recruits with true and misconceived food allergy. This data reflects the information gathered from the time of initial evaluation until enlistment.

*$p < 0.005$.

a misbelief of food-allergy, and that these individuals suffer from a high rate of anxiety disorders, come from a lower educational background, and are mostly of female sex. Given the high rate of falsely believed food allergy, it is imperative to improve medical awareness and educational programs regarding the nature of food allergy in order to prevent the potential emotional, nutritional and social burden of misconceived food allergy.

A significantly higher rate of reported food allergy compared to true food allergy is a finding shared by many epidemiological studies [13,15–17]. The rate of misconceived food allergy in our study was high as well, reaching 43% of recruits reporting food allergy [20]. Still, this rate is lower than most previous studies [13,15–17]. This finding may partly be attributed to inherent differences in study populations, but might also reflect differences in the research methods used. One study used food diaries in addition to the regular question for participants: "Do you have any food allergies?". The authors found that in 5–34% of cases the reported allergenic foods were regularly included in patients' diet [19]. Participants in our study were interviewed face-to-face by qualified physicians, reducing incorrect reporting of food allergy. More importantly, we used an opening question not only asking about allergy to foods but also requiring their avoidance. This enabled us to identify the population that is most likely impaired (nutritional deficiencies, social isolation, reduced activities and increased economic burden) by either true or misconceived food allergy [3,8,9,12].

Several previous studies described higher prevalence of anxiety and depression among food allergic patients while others reported increased vigilance only [9–12,26]. This variability may be partially related to the various age groups studied or to different research methods used. Regardless, these findings rely only on participants' self-report. Interestingly, we found a higher rate of anxiety disorder primarily in individuals who mistakenly believed they were food-allergic but not in true food allergic patients. It is likely that patients with misconceived food allergy had pre-existing anxiety which might have contributed to their misbelief. Of note, in some of these patients, the anxiety disorder manifested itself close to their enlistment day, likely due to the stressful impact of upcoming enlistment. Moreover, some of these patients still claimed to have food allergy months after it was ruled out, necessitating additional allergy evaluations to convince them. Patients suffering from anxiety disorders often complain of symptoms that are typical of other medical conditions, resulting in delayed diagnosis and treatment [27]. Primary care physicians and allergists' awareness of potential anxiety disorder is mandatory for proper diagnosis and management of these patients [27]. Together with the fact that most of these recruits had never been consulted by an allergist, these finding further emphasizes the importance of primary care physicians in timely referral of these patients for allergy evaluation.

We found significantly higher Cognitive Scores in recruits with true food allergy compared to participants who did not report food allergy. This is in line with a previous finding of higher Cognitive Scores in recruits with asthma, another atopic disease, in the same population of Israeli military recruits [24]. Given the correlation between Cognitive Scores and socioeconomic status, this finding might reflect the effect of the hygiene hypothesis (more crowded living conditions and larger families) [1,28–32]. In contrast, teenagers with misconceived food allergy had lower Combined Intellectual-Education scores, a score that is affected also by the level of education. Moreover, most of these recruits had never been consulted by an allergist, although this service is widely available without financial limitation for the entire Israeli population. These findings suggest that better educational programs regarding the nature of food allergy are required [33], particularly in populations from lower educational levels.

During pre-adolescence, boys are more often affected than girls by atopic conditions such as asthma and food allergies. In contrast, later in life females and males suffer equally from hay fever, while females have significantly more food-induced complaints. Several factors, such as hormonal effects, gender-specific behavior, perception of risk, or intake of medications were postulated to account for these observations [34]. However, this specific food allergy female predominance is driven by questionnaire-based surveys [19,34–35]. Our findings suggest that the observed self-reported female predominance in adolescence might reflect misconceived rather than actual food allergy.

A longer time was required to rule-out misconceived food allergy than to verify true food allergy. This might reflect the need for OFCs in many of these recruits or the fact that it took them longer to comply with evaluation recommendations. Moreover, additional allergy evaluations were required to convince some of these patients that they are not food allergic, emphasizing that false belief of food allergy requires significant resources from the medical system.

Atopic co-morbidities are widely reported, as expected, in patients with food allergy [6,7,28]. Interestingly, we found increased prevalence of atopic diseases also among recruits who mistakenly believed they have food allergy. While it is possible that having atopic co-morbidities led these individuals to attribute certain unrelated symptoms also to allergy to foods, this association requires further investigation. Increased attention to, and proactive questioning of any suspected food allergy among allergists and physicians caring for atopic patients may prevent some cases of food allergy misconception and reduce patient anxiety.

This study has several limitations. First, it reflects a distinct population in ethnicity, geographical location, and age range and these variables have been shown to have an effect on the epidemiology of food allergy [36]. Second, the information provided for some of the medical conditions was retrospective. Still, the diagnosis of food allergy, psychiatric disorders, conditions which required supporting laboratory data, and the Cognitive and Combined Intellectual-Education scores were made by current and objective criteria. Malingering could have potentially lead to misreported food allergy. However, at the time of the study there were no restrictions on military service conditions for food allergic patients. Therefore, the risk of false reports of food allergy for secondary gain was low. Lastly, follow up during the period between initial medical evaluation and enlistment was not available for recruits with no reported food allergy.

In summary, this study highlights the importance of correct diagnosis of patients with misconceived food allergy. The higher rate of anxiety disorders in these patients, together with the lower educational background and the lack of previous appropriate allergic evaluation, suggests that better education, and medical awareness are needed to better address these patients' psycho-social burdens.

Declaration Of Competing Interest

There are no reported conflicts of interest for any of the authors.

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Data Sharing Statement

De-identified participant data (including data dictionaries) will not be shared, as this data is confidential under the regulations of the Israeli Defense Forces.

Author Contributions

Liat Nachshon, Arnon Elizur and Naama Schwartz contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, and drafting the article. Michael Goldberg and Yitzhak Katz contributed to acquisition of data, analysis and interpretation of data, and drafting the article. Yossi Schon and Michael Cheryomukhin contributed to acquisition of data and drafting the article.

Liat Nachshon, Naama Schwartz and Arnon Elizur had full access to the full data in the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.100766.

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Supplementary Materials

Supplementary methods

Intellectual score assessment

The cognitive score assessment is composed of four subtests: [1] arithmetic, assessing reasoning, concentration, and concept manipulation; [2] similarities, assessing verbal abstraction and categorization; [3] Nonverbal abstract reasoning and problem solving abilities assessed by a multiple choice measure modified version of Raven's Progressive Matrices (1); and [4]ability to understand and carry out verbal instructions measured by a modified, Otis type, verbal intelligence test of mental ability, adapted from the U.S. Army Alpha Instructions Test (2). Each of these four results were amalgamated and rounded-up to give one of nine possible scores (10 lowest, 90 highest).

Combined intellectual-education score

The combined intellectual-education score is composed of three variables**:** [1] education (comprising 17%), based on years at school, the educational institution, type and level of studies, and grades; [2] the Intellectual Score (comprising 50%); and [3] a personal interview (comprising 33%). The final score ranges from 41 (low) to 56 (High).

Skin Prick Test (SPT) and oral food challenge (OFC) performance

SPT's were performed on the volar surface of the forearm with single peak lancets (Heinz Herenz, Hamburg, Germany) using commercial extracts whenever available (1:10 w/v Alk-Abello, Port Washington, New-York) and fresh foods in all other cases. In cases of suspected tree-nut or sesame allergy, locally produced standardized high protein extracts were used (3, 4). Histamine 1 mg/mL (ALK-Abello) and saline were used as the positive and negative controls, respectively. The wheal and flare sizes were measured after 15 minutes. OFCs were performed according to previously published protocols (5) to patients who met one of the following criteria: (a) Had no history of an allergic reaction to the suspected food/s during the past two years; (b) The reported reaction to the suspected food included symptoms that were not entirely consistent with FA such as symptoms that either developed greater than 2 hours after the food ingestion or appeared additionally without food exposure, or included only perioral complaints; (c) Reported of typical signs and symptoms of FA without evidence for IgE reactivity to the suspected food. A challenge was considered positive if objective skin rash, upper respiratory, lower respiratory, conjunctival congestion or gastrointestinal symptoms appeared during the challenge and up to 2 hours after the last dose.

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