**Appendix 1**

Most adolescents in Israel are obliged to service by law. The main populations which do not present themselves at local recruitment centers for medical examination and profiling, and are exempt from service, females (who are married, pregnant or mothers), religious populations (while orthodox Jewish males can postpone their service, females can be released based on testimony to their religious lifestyle), and minorities (only Druze and Circassian males are obliged to service by law, whereas males of other minorities can volunteer. Females of all minorities are exempt from service.) Therefore, these (mainly female) populations are under-represented in this cohort. Consequently, findings among females are expected to relate mainly to the Jewish secular to traditional sectors.

**Appendix 2**

The medical process at the recruitment center involves preliminary documentation from the primary care physician at his/her health maintenance organization, and examinations that include blood pressure, pulse rate, visual acuity, and color vision testing all performed by trained medical personnel. Weight and height are measured by trained technicians. The same models of altimeters and scales are used and instruments are calibrated and checked for accuracy by experienced technical personnel at regular intervals. Urinalysis is performed with a dipstick and read by a laboratory technician. If the dipstick analysis is abnormal, the urine sediment is examined by high-power microscopy. Abnormal findings in urine microscopy warrant further investigation. Examination by the physician at the recruitment center includes a systematic and thorough anamnesis including family history, habits, psychological evaluation, complete physical examination and referral if necessary for further investigation according to findings. Finally, a profile and appropriate Functional Classifications Codes (FCCs) that describe medical status (condition and severity) are assigned. The FCCs are organized in sections dealing with medical conditions in the standard profiling manual used for Israeli Defense Force recruits and soldiers.

The computerized medical database contains further personal and demographic information about each recruit, as recorded by the Ministry of Internal affairs and validated (and updated) by interview and questionnaire. The data consist of identity number, date of birth, date of arrival to Israel (if not born in Israel), country of origin, determined by paternal country of origin, gender, religion, exact date of birth (verified by records of the Ministry of Internal Affairs), parental ages and place of residence. Further data include number of years of education as verified by personal interview and by documentation from the educational institution, intelligence score as determined by a personal psychometric test, number of children in the family and the recruit’s place among them, and parent’s occupations.

There are various parameters that represent different aspects of education. The main one, used in this study, takes into account the number of years of study, the course of study and the highest level of educational institution.

**Appendix 3**

As this study is also aimed at providing an overarching characterization of the medical conditions associated with cardiac anomalies groups, diverse medical conditions were grouped together, while focusing key anthropometric parameters and on the more common medical conditions among conscripts. The following definitions were used (alphabetic order):

Anthropometric parameters

***Blood pressure (BP) definitions***: Systolic and diastolic BP measures (herein SBP and DBP, respectively) were obtained by a sphygmomanometer, in a relaxed, sitting position. Categories were defined following age-adjusted (17 years old)- and height adjusted (174 cm and 162 cm for males and females, respectively)- definitions of the Ministry of Health. Six categories were defined hierarchically based on clinical severity: missing BP, either DBP=0 or SBP=0; Abnormal BP: either DBP=1-39 or SBP=1-79 or SBP-DBP<20; Hypertension type II (>99th percentile + 5 mmHg): either DBP>90 or SBP>146/139 or males/females or recruits belonging to 1 of the 3 BP categories indicated below and having FCC indicative of taking medications due to hypertension type II; hypertension type I (≥95th percentile and ≤99th percentile + 5 mmHg), DBP=86-90 or SBP=135-146/129-139 for males/females; pre-hypertension (≥90th percentile and <95th percentile + 5 mmHg), DBP=80-85 or SBP=120-134/120-138 for males/females; hypotension: DBP=40-49 or SBP=80-89; normal BP, DBP=50-79 or SBP=90-119. Diagnosis of hypertension also warranted further workup, including ten blood pressure measurements on alternate days, renal function tests, eye fundus examination and cardiac transthoracic echo. Lipid profile, blood glucose, BMI and family history of cardiovascular disease were also examined to access risk factors.

***BMI definitions:*** BMI groups were defined according to gender-related percentiles for 17 years old BMI on growth charts of the Israeli Ministry of Health: Obesity - above the 95th percentile (>28.2 kg/m² and >29.6 kg/m² for males and females, respectively); Overweight - the 85th-95th percentiles (25.0-28.2 kg/m² and 25.2-29.6 kg/m²); Underweight - below 5th percentile (<17.6 kg/m² and <17.2 kg/m²). The age of 17 years was chosen as the median age [and interquartile range] of males and females was 17.35 [17.08-17.9] and 17.24 [17.02-17.63], respectively. A similar approach is used by the U.S. Centers for Disease Control and Prevention ([1](#_ENREF_1)). As opposed to the International Obesity Task Force definitions ([2](#_ENREF_2), [3](#_ENREF_3)), it includes also the underweight group, which is of interest in this study.

***Height definitions:*** Height was divided into percentiles according to the growth charts of the Israeli Ministry of Health individually for males and females aged 17 years old. Low was either <5th or <10th percentiles of height, whereas as High the >90th or >95th or >99th percentiles of height were considered.

Medical conditions

***Allergic rhinitis***: Diagnosis was made according to previous documentation verified by ear, nose and throat specialist or allergy specialist. Diagnosis required chronic rhinitis associated with allergens and/or season of year.

***Asthma***: Asthma diagnosis was established by previous medical documentation from the primary physician and thorough anamnesis, physical examination, and by spirometry results together with expert pulmonologist examination. Only active asthma was included in the present analysis (wheezing, chronic cough, dyspnea on effort and or upon exposure to allergens less than three years before examination period).

***Cardiac anomalies***: Cardiac anomalies were diagnosed according to specialist cardiologist examination and Echo Doppler study. Cardiac anomalies included valvar abnormalities such as bicuspid aortic valve, aortic valve insufficiency or stenosis, mitral valve insufficiency or stenosis, pulmonary stenosis or insufficiency, tricuspid valve insufficiency or stenosis. Non-vallar anomalies included patent ductus arteriosus, atrial septal defect, ventricular septal defect, coarctation of aorta, Tetralogy of Fallot, Complete transposition of great vessels and dextrocardia.

***Color blindness:*** Color vision was examined using Ishihara colored charts .Color vision defect was established if the person examined failed to read 6 or more colored chart correctly.

***Diabetes mellitus***: Diabetes mellitus diagnosis was established by fasting blood glucose levels above 126 mg/dL for those examined after 1998, and above 140 mg/dL for those examined during previous years in repeated analysis, and or two hour post- prandial glucose levels above 200 mg/dL. The change in fasting glucose levels threshold was made according to changes in definition as decided by WHO and NIH.

***Endocrine disorders***: Endocrine disorders were diagnosed by specialist endocrinologist according to accepted criteria and included mostly thyroid gland disease, hormonal deficiencies, adrenal gland disorders, diseases of pituitary gland, and parathyroid disorders.

***Flat feet***: Flat feet assessment included anamnesis and examination in standing position, standing on toes and assessment of foot arch flexibility, along with sub-talar movement and existence of valgus of heels at standing position. Only severe flat feet were included in analysis.

***Hearing problems:*** Hearing loss was defined by audiometry and a specialist ENT examination. Hearing loss included conductive, sensori-neural and mixed type.

***Hematological malignancy***: Hematological malignancies were diagnosed at hemato-oncological units and included exact histopathology, stage and grade, bone marrow biopsy results, treatment protocols (chemotherapy, radiation, biological treatment, bone marrow transplant, etc.). Hematological malignancies included mainly acute leukemias (mostly ALL) and Hodgkin and non-Hodgkin lymphomas.

***Hyperlipidemia***: Hyperlipidemia was diagnosed as low-density lipoprotein (LDL) cholesterol levels above 150 mg/dL and/or triglyceride levels above 200 mg/dL.

***Knee disorders***: Knee disorders were verified by an orthopedic surgeon, and included: chondromalacia of patellae, meniscal derangements and partial or complete ligament tears as diagnosed by an orthopedic surgeon.

***Learning disorders/ADHDs***: Learning disabilities and attention-deficit disorder (ADD) / attention-deficit hyperactivity disorder (ADHD) were diagnosed by specific psycho-diagnostic tests and verified by neurologist and or psychiatrist examination. In this analysis, only the severe learning disorders were included, such as those accompanied by dyspraxia or coordination problems, or severe ADD/ADHD requiring daily consumption of medication (Ritalin or Concerta).

***Mental disorders***: Mental disorders were diagnosed by a specialist psychiatric and severities were established according to criteria of the 10th revision of the international classification of diseases (ICD)-10 of the world health organization (WHO). Mental disorders included personality disorders, neuroses, adjustment disorders, post- traumatic stress disorders, psychosis, mood disorders, mental retardation, pervasive developmental disorders, eating disorders, somatoform disorders, alcohol and drug abuse.

***Micro-hematuria***: Isolated microscopic hematuria diagnosis was described in detail elsewhere ([4](#_ENREF_4)). Briefly, definition was based on three urine sample analysis in succession with positive dipstick for blood and microscopic analysis of urinary sediment containing three or more erythrocytes per high power field examination, with a workup that included imaging of kidneys and urinary bladder, renal function test and a specialist nephrologist verification of diagnosis. It is also important to state that only isolated microscopic hematuria cases were included as assessed by the urine results in the computerized database. Only those who had both positive blood urine according to the database and a specific FCC that indicated diagnosis of isolated hematuria were included in analysis.

***Migraine***: Diagnosis of migraine relied on at least one-year documentation of headaches with typical characteristics of migraine, which was verified by a neurologist.

***Proteinuria***: Proteinuria was defined as three successive urine samples containing positive protein according to dipstick analysis, and the amount of more than 200 mg protein in 24 hour urine collection, along with normal imaging of kidneys and bladder and normal renal function tests, plus having a specific FCC that indicated proteinuria diagnosis. Diagnosis was verified by a nephrologist.

***Refractive errors***: Refractive errors were determined by eyesight examination by a trained technical personnel and establishment of a refractive error by further examination by an optometrist or ophthalmologist. Those included myopia, hypermetropia, anisometropia, amblyopia and astigmatism. Severity was determined by the finding of refraction and visual acuity after correction as well as assignment of FCC.

***Scoliosis/Kyphosis***: Spine deformities included scoliosis and kyphosis as established by clinical examination and X- ray imaging.

***Sleep disorders***: Sleep disorders included mainly sleep apnea syndrome and somnambulism diagnosed at a certified sleep disorders laboratory and verified by sleep disorders specialist.

***Solid malignant tumors***: Malignant solid tumors diagnosis was made by oncologists and verified by documentation from hospitals, oncological units, including histopathology, stage, grade, treatment protocols, clinical course, involvement of other organs and/or side effects of chemotherapy/radiotherapy and present condition. Solid malignancies included Wilms' tumor, neuroblastoma, testicular tumors, sarcomas, malignant brain tumors, gynecological malignancies among females, epithelial tumors etc.

***Urogenital malformations***: These were diagnosed by imaging ultrasonography and urology specialist examination. Those included fusion of kidneys, horseshoe kidney, pelvic kidney, hypoplastic kidney, single kidney, vesico- ureteral reflux, double ureter, megaureter, double collecting system, hydronephrosis, urinary bladder malformations, hypospadias, epispadias, UPJ stenosis, urethral stenosis.

**Appendix 4**

Of interest and possible importance, albeit consisting of only four cases, is the novel positive association between "endocrine" (predominantly thyroid and/or growth abnormalities) disorders and significant valvar anomalies. Although a strong relationship between chronic thyroiditis and MVP has previously been shown ([5](#_ENREF_5)), no relationship between endocrine disorders and MVP was found in this study. Future studies may shed more light on this issue.

Although with only one case, the positive association of diabetes mellitus with the significant structural group is intriguing as there is a recent large population based study showing an increased risk of developing type 2 diabetes mellitus in subjects with congenital heart disease after they reach the age of 30 years ([6](#_ENREF_6)). In an echocardiographic study of young patients who were normotensive with type 1 diabetes, significant structural and functional abnormalities were found but with only 56 patients with this condition, it was probably too small to find any congenital heart abnormalities ([7](#_ENREF_7)). It is known that maternal diabetes may be teratogenic with a higher risk of congenital heart disease in the fetus ([8](#_ENREF_8)). As diabetes runs in families it may well be a contributing factor to higher prevalence of significant structural abnormalities ([9](#_ENREF_9)). However, it is unknown whether a familial predisposition to diabetes in addition is related to cardiac anomalies.

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