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Screening for obesity in the offspring of first-cousin consanguineous couples: A Phase-I study in Saudi Arabia

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ABSTRACT

Consanguineous or cousin marriages are very common in Saudi Arabia. However, owing to limited studies and insufficient knowledge about genetic diseases/disorders, many couples are unaware of the increased health risks for their offspring. Among the inherited and complex diseases from parents' consanguinity, obesity is common; therefore, we examined the prevalence of obesity in the offspring of first-cousin consanguineous couples in Saudi Arabia. In this questionnaire-based study, 657 individuals (mean age = 18.7 ± 10.2 years; age range = 2–65 years) who were residing in Riyadh, Saudi Arabia participated. Among them, almost 90% were native Saudis. Participants mean body mass index (BMI) was 24.5 ± 9.1 kg/m2. Sex- stratified demographic details confirmed a significant association between age and BMI (p < .001). We confirmed that adolescents and adults were more prone to develop obesity. Adults and non-Saudi participants were three times more likely to develop obesity if they had first-cousin consanguineous parents than those who did not. Of the 30% of participants who were obese, 100 will be selected for Phase II, in which we plan to perform exome sequencing.

1. Introduction

Obesity is the result of fat storage that takes place naturally in the body due to a lack of exercise or an uncontrolled diet (Fitzpatrick et al., 2018). After some controversy, obesity has been confirmed as a human disease (Müller and Geisler, 2017). Obesity is defined as a body mass index (BMI) $\geq 30\,kg/m^2$. Obesity is caused by energy imbalance: when the energy gained from calories is greater than the energy expended from physical activity; the body stores the extra calories as fat (Alharbi et al., 2017). There is an increased prevalence of being overweight and obesity globally (Isakova et al., 2018). Per the World Health Organization (WHO), the global prevalence of obesity in adults is 13%, and it is 18% in children aged 5–19 years (Aguayo-Armendáriz et al., 2018). In gulf countries, the obesity prevalence is 5–14% in children and adolescents. Notably, the obesity prevalence in Riyadh, the capital city of Saudi Arabia, is 22% (Al-Ghamdi et al., 2018). Further, the highest global prevalence of obesity in women is in Saudi Arabia (Alharbi et al., 2017).

Earlier genetic and non-genetic studies have confirmed obesity as a multifactorial/heterogeneous disorder (Lin et al., 2018) with a polygenic etiology (Aguayo-Armendáriz et al., 2018). Obesity leads to medical complications such as type 2 diabetes mellitus, hypertension, stroke, coronary heart disease, cardiovascular disease, gall bladder disease, metabolic syndrome, pulmonary disease, osteoarthritis, non-alcoholic fatty liver disease, and cancers (Ben Halima et al., 2018). However, calorie-dense food and a sedentary lifestyle alone do not seem to explain this phenomenon in it's entirely (Watanabe et al., 2018).

Consanguinity implies the inheritance of genes that are inherited from common ancestors; it is a social and genetic concept that usually denotes reproductive association between closely related individuals (Verweij et al., 2014). Consanguineous marriages are very common in the Middle East, including Saudi Arabia (Bener et al., 2007). Although, the prevalence of consanguinity varies across populations, the rates are not well documented. Examining

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consanguineous families has played a key role in determining the genetic basis of several heritable diseases and researchers have gained insight into major molecular mechanisms governing physiological processes (Saeed et al., 2018). Consanguinity is defined as a biological relationship within a family. The marriage between a related man and woman is known as consanguineous marriage, and it has been practiced for thousands of years globally. Consanguinity is a deeply rooted social trend, and more than 1.2 billion of the world population are consanguineous couples. Globally, approximately 20% of marriages are consanguineous (Al-Mousa and Al-Saud, 2017), which are common for socio-economic, ethno-cultural, geographic, and religious reasons (Warsy et al., 2014).

Recently, researchers have examined how consanguineous marriages are related to human health (Fareed and Afzal, 2017). Consanguineous marriages can lead to an increase in the frequency of homozygous genotypes, which allows the less common alleles to manifest as homozygous (Mokhtar and Abdel-Fattah, 2001). Risk of genetic disorders may be inherited among common ancestors due to the expression of autosomal recessive gene mutations. Problems occur because of the biological relationship between parents; therefore, there is an enhanced possibility that their offspring will inherit identical copies of detrimental recessive genes (Shawky et al., 2013). An earlier study Becker et al. (2001) confirmed that first-cousin consanguinity is significantly associated with congenital heart disease in Saudi Arabia. However, to date, no studies have examined the correlation between consanguinity and obesity. The lifestyle in Saudi Arabia has changed dramatically with the increase in wealth due to oil discovery. Further, Bosdou et al. (2016) confirmed the connection between obesity and infertility in consanguineous women; i.e., due to an elevated BMI, women's hormone abnormalities and ovulation dysfunction can lead to infertility. Therefore, we examined the BMI and health-related characteristics of the offspring of first-cousin consanguineous couples.

2. Material and methods

Ethical approval (CAMS 01/3536) was granted from the College of Applied Medical Sciences, King Saud University (KSU), Riyadh, Saudi Arabia. In this retrospective study, we collected data from 657 individuals living in Riyadh city, Saudi Arabia from February 2015 to December 2017. Specifically, participants were recruited from Sahara Mall, Saudi boys' school, King Khalid University Hospitals, and KSU medical college. All participants completed the questionnaire and provided written consent.

Inclusion criteria were based on the obese or non-obese offspring of consanguinity couples. Exclusion criteria were offspring of non-consanguineous couples and siblings of consanguineous couples. As per the WHO's criteria (WHO, 2016), obese participants were categorized into three groups based on age: (i) childhood obesity (aged 0–4 years), (ii) adolescent obesity (aged 5–19 years) and adult obesity (aged $\geq$ 19 years). Childhood obesity was calculated as >3 standard deviations (SDs) for weight/height; for overweight, it was >2 SDs for weight/height. Adolescents' obesity was calculated as >2 SDs as per the WHO growth reference median; overweight was BMI for age >1 SD above the WHO growth reference (WHO, 2016). For adults, a BMI $\geq$ 25 kg/m^2 or $\geq$30 kg/m^2 were categorized as overweight or obese, respectively.

The study purpose was well explained in both Arabic and English. The questionnaire included the following anthropometric measurements: age, weight, height, BMI, nationality, and family history of consanguinity. Simultaneously, with trained nurses, we collected saliva samples from each patient to process genomic DNA. The structured questionnaire was finalized by three experts based on their experience. BMI was calculated as weight in kg and height in cm or meters squared (Alharbi et al., 2017).

2.1. Statistical analyses

Collected data were shifted to Excel and statistically analyzed using R software. Continuous data were presented as means and SDs; categorical data were obtained as frequencies and percentages (%). Independent sample t-tests and analyses of variance were used to determine the significant mean difference between groups. Chi-square tests were used to determine differences in proportions between categorical variables. Furthermore, a logistic regression analysis was used to determine the odds of being obese against potential risk factors. P < .05 was considered significant.

3. Results

Participants' (N = 657) demographic characteristics are shown in Table 1. Table 2 describes participants' demographic characteristics per sex. There were significant sex differences in age, height, BMI, and nationality. Weight, obesity, and having other diseases failed to show significant sex differences. Table 3 describes participants' demographic characteristics per age. We found significant age differences for all key study variables. Table 4 describes participants' demographic characteristics per whether they were obese. We found significant differences for all key study variables, except sex. Table 5 presents the risk factors for obesity. Adults were significantly more likely to be obese compared to adolescents and non-Saudis were 3 times more likely to have obesity as compared to Saudi participants. Figs. 1 and 2 (Supplementary files) represent the association between BMI and age across both sexes for those aged 2–19 years.

Table 1
Participants' demographical details.

Demographic variables	Mean ± standard deviation or n (%)
N	657
Age (years) (range = 2–65 years)	18.7 ± 10.2
Male	376 (57.2)
Weight (kgs)	59.6 ± 28.0
Height (cms)	153.0 ± 20.0
Body mass index (kg/m^2)	24.5 ± 9.1
Saudi nationality	589 (89.6%)
Obese	193 (30.0)
Other diseases	41 (6.2%)
Family history of consanguinity	657 (100%)

Note: Data presented as Mean ± SD for continuous normal variables whereas categorical variables are presented as N (%). P-value < .05 considered significant.

Table 2
Descriptive statistics per sex.

Demographic details	Male (n = 376)	Female (n = 281)	P value
Age (Years) (2–65)	16.4 ± 8.0	21.7 ± 11.9	<.001
Weight (kg)	60.3 ± 28.4	58.7 ± 27.4	.463
Height (cm)	155.9 ± 19.9	148.4 ± 18.4	<.001
BMI (kg/m^2)	23.6 ± 8.1	25.7 ± 10.3	.005
Saudi nationality	347 (92.3)	242 (86.1)	.010
Obesity	103 (27.7)	90 (33.1)	.140
Other diseases	21 (5.6)	20 (7.1)	.422
Family history of consanguinity	376 (100)	281 (100)	–

Note: Data presented as Mean ± SD for continuous normal variables whereas categorical variables are presented as N (%). P-value < .05 considered significant.

Table 3
Descriptive statistics per age groups.

Demographic details	Child (0–4) (n = 19; 2.9%)	Adolescent (5–19) (n = 432; 65.8%)	Adult (>19) (n = 206; 31.4%)	P Value
Age (Years)	3.4 ± 0.8	13.5 ± 3.6[a]	30.9 ± 8.7[ab]	<.001
Male	8 (44.4)	302 (69.9)[a]	66 (32.0)[b]	<.001
Weight (kgs)	16.3 ± 3.7	52.0 ± 23.6[a]	79.2 ± 25.9[ab]	<.001
Height (cms)	95.5 ± 13.7	150.7 ± 18.7[a]	161.5 ± 11.3[ab]	<.001
BMI (kg/m^2)	19.5 ± 10.5	21.9 ± 6.9[a]	30.4 ± 10.3[ab]	<.001
Saudi Nationality	12 (66.7)	398 (92.1)[a]	178 (86.4)	<.001
Obesity	5 (33.3)	97 (22.7)[a]	91 (45.0)[ab]	<.001
Other diseases	3 (16.7)	14 (3.2)[a]	24 (11.7)[b]	<.001
Family history of consanguinity	18 (100.0)	432 (100.0)	206 (100.0)	–

Note: Data presented as Mean ± SD for continuous normal variables whereas categorical variables are presented as N (%). P-value < .05 considered significant. [a]indicates significantly different from child; [b]indicates significantly different from adolescents and [ab]indicates significant difference from both child and adolescent.

Table 4
Descriptive statistics according to Obesity status.

Demographic details	Obese	Non-Obese	P Value
n	193 (30.0)	451 (70.0)	
Age (years)	23.1 ± 12.5	16.8 ± 8.2	<.001
Male	103 (53.4)	269 (59.6)	.140
Weight (kgs)	86.7 ± 28.4	48.3 ± 18.1	<.001
Height (cms)	156.3 ± 19.4	151.3 ± 19.3	<.001
Body mass index (kg/m^2)	34.8 ± 9.2	20.1 ± 4.2	.003
Saudi Nationality	158 (81.9)	422 (93.6)	.001
Other diseases	19 (9.8)	20 (4.4)	<.001
Family history of consanguinity	193 (100.0)	451 (100.0)	–

Note: Data presented as Mean ± SD for continuous normal variables whereas categorical variables are presented as N (%). P-value < .05 considered significant.

Table 5
Risk factors as per obesity.

Demographics	OR (95% CI)	P-value
Age		
Child (0–4 years)	0.47 (0.15–1.48)	.196
Adolescent (5–19 years)	0.36 (0.24–0.54)	<.001
Adult (>19 years)	Reference	
Sex		
Male	1.17 (0.80–1.72)	.417
Female	Reference	
Nationality		
Saudi	0.32 (0.19–0.56)	<.001
Non-Saudi	Reference	
Other disease		
Yes	1.71 (0.85–3.42)	.131
No	Reference	

Note. Data presented as Odds-ratio. P-value < .05 considered significant.

4. Discussion

Obesity is a worldwide problem that affects both children and adults across both sexes (Azzeh et al., 2017). Obesity is defined as a complex, chronic, multifactorial disease caused by nutritional imbalance with or without genetic and endocrine-metabolic disorders (da Silva et al., 2018). The current study was designed as an initial screening of the offspring of first-cousin parents in Saudi Arabia.

We revealed that 30% of the participants were obese. Adolescent and adult participants were prone to develop obesity based on their current BMIs. Since 1975, the prevalence of global obesity has tripled to 671 million in adults and 124 million in young people (aged 5–19 years) (Ells et al., 2018). Per the WHO (WHO, 2016), there are about 42 million overweight children aged younger than five years (Al Dhaifallah et al., 2015). Being overweight and obesity during childhood is associated with obesity in adulthood and a wide range of chronic diseases at a younger age such as cancer, diabetes, hypertension, cardiovascular disease, sleep apnea, and musculoskeletal conditions (Villarosa et al., 2018). Prior studies have confirmed a strong association between consanguineous offspring and genetic disorders/diseases, especially compared with non-consanguineous couples (Alnaqeb et al., 2018), including being prone to cancer (Jastaniah et al., 2018). Earlier studies also documented that parental consanguinity can lead to many multiple diseases, further highlighting the need for the present study. Common most categories of consanguineous unions are defined as first-cousin union, due to the closest genetic/inherited connection between the couples which can leads to identical copies of damaging recessive alleles (Hosseinpour et al., 2016).

Genetic background plays a major role in understanding any disease/metabolic pathways that regulate obesity (Speakman et al., 2011). Without the involvement of Mendelian inheritance, obesity has a strong connotation with genetics (Sheikh et al., 2017). Cytogenetic analysis cannot justify all human diseases; however, molecular genetics will be helpful for disease diagnosis and prediction, which will be useful for treatment selection and concern therapies. Prior to exome sequencing studies, candidate gene, case-control, family/hospital based, monogenic, meta-analysis, and genome wide association studies have confirmed the risk of obesity; however, they do not provide accurate information regarding diagnoses (Xia and Grant, 2013). Global studies have also failed to show the connection between disease-causing genes and genetics (Mehrad-Majd et al., 2018; Ritter et al., 2018). Exome sequencing can also enable sequencing of all protein-coding regions in the human genome. This powerful sequencing methodology can be a cost-effective tool for dismembering genetic and monogenetic diseases. The functional application of exome sequencing is reformed to discover the rare alleles in heritability of complex diseases and health-related traits (Bamshad et al., 2011).

The initial success of the whole exome sequencing technique concerned inflammatory bowel disease, including identification of a rare variant, which was useful for diagnosis and treatment in infants (Warr et al., 2015). Erzurumluoglu et al. (2016) recommended that consanguineous offspring should be analyzed without clinical phenotypes to detect for specific genes dock mutations in the homozygous loss of proteins.

The relationship between the offspring of first-cousin consanguinity and obesity has not been documented; however, other diseases have been recognized (Rudan et al., 2003; Stoltenberg et al., 1999). Although numerous global studies have examined child and adult obesity (e.g., Ahmad et al., 2018; Eldosouky et al., 2018; Ibrahim et al., 2017), limited genetic and non-genetic studies have addressed the Saudi Population (Alharbi et al., 2017; Al-Daghri et al., 2016; Alharbi et al., 2014). To date, no studies have examined first-cousin obesity/non-obesity offspring in the Saudi population.

Strength of this study is that almost 90% of our participants were from Saudi, and this study was performed in Riyadh, Saudi Arabia. A limitation of this study was not examining family pedigree and other demographical details. We also did not recruit the offspring from second cousins. In conclusion, adolescent and adult participants were more prone to develop obesity than were children. Adult and non-Saudi offspring of first-cousin consanguineous parents were three times more likely to develop obesity than were their counterparts. Of the 30% of participants who were obese, 100 will be selected for Phase II, in which we plan to perform exome sequencing. Future studies should be conducted with other cultures. Consanguineous couples should seek genetic counseling to minimize any risks for their children.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sjbs.2019.09.001.

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