The Egyptian Journal of Medical Human Genetics 18 (2017) 315–320

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Contents lists available at ScienceDirect

The Egyptian Journal of Medical Human Genetics

journal homepage: www.sciencedirect.com

Original article

Global distribution of consanguinity and their impact on complex diseases: Genetic disorders from an endogamous population

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ARTICLE INFO

Article history:
Received 12 January 2017
Accepted 29 January 2017
Available online 20 February 2017

Keywords:
Consanguinity
Inbreeding
Global impact
Complex diseases
Counseling

ABSTRACT

Background: Marriage between close relatives has been practised globally since the early existence of human society. The role of consanguinity and inbreeding affecting human health is a topic of great interest in medical genetics.

Objective: The objective of the study was to investigate the extent of consanguinity and its effects on common non-communicable diseases, the related risk factors, its role in human health and susceptibility to various chronic and complex diseases in Qatari population.

Subjects and methods: The study design was a cross-sectional and multi-stage sampling based on Hospitals and primary health care [PHC] centres. A representative sample of 1626 subjects were approached and 1228 subjects (75.5%) consented to participate in the study between January 2013 and May 2014. The questionnaire based on socio-demographic data and for responses, on the Premarital Screening and Genetic Counseling [PMSGC] program knowledge, attitude and practice statements. Additionally, questions were asked regarding services, activities, how to attract and motivate the genetics counseling and screening for the hereditary diseases programme.

Results: The mean age ± S.D of the 1228 women interviewed was 39.25 ± 9.57 years. The rate of consanguinity in the present generation was 43.5% [95% CI = 47.7–54.4]. There were statistically significant differences between males and females with regards to age, educational status, occupation status, household income, consanguinity, BMI, cigarette smoking and sheesha (water pipe) smoking. The consanguinity rate and coefficient of inbreeding in the parental was significantly higher than the maternal rate (44.3% versus 41.4%; $p < 0.001$) (0.018738 versus 0.017571 maternal). The current generation of consanguineous parents had a slightly higher risk for diseases such as diabetes mellitus, cancer, blood and mental disorders, heart diseases, asthma, gastro-intestinal disorders, hypertension, hearing deficit, G6PD and common eye diseases.

Conclusion: The present study revealed a higher incidence of certain diseases in consanguineous population with a high significant increase in the prevalence of common adult diseases such as diabetes mellitus, cancer, blood disorders, mental disorders, heart diseases, asthma, gastro-intestinal disorders, hypertension, hearing deficit, G6PD and common eye diseases. This confirms the role of genetic factors across the full spectrum of disease and not only for Mendelian disorders.

1. Introduction

Consanguineous marriages have been practiced since the early existence of humans. At present, accounting for 20% of world populations live in communities with a preference for consanguineous marriage [1–3]. Consanguinity rates vary from one population to another, varying with differences in religion, culture and geography [3–8]. A number of factors govern the influence of endogamy on community gene pools. There is an important cluster of countries with high levels of consanguinity observed in most communi-

Peer review under responsibility of Ain Shams University.

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http://dx.doi.org/10.1016/j.ejmhg.2017.01.002
1110-8630/

ties of North Africa, the Middle East and Western Asia, a transverse belt that runs from Pakistan and Afghanistan in the east to Morocco in the west, and also in South India, with intra-familial unions collectively accounting for 20−50+% of all marriages [3–8]. Noticeably, many Arab countries display some of the highest rates of consanguineous marriages. The rate of consanguineous marriage varies in different countries and is usually associated with demographic features, such as religion, educational level, socioeconomic status, geography (including urban/rural community, size of the area, isolation of the population), consanguinity among the parents' marriages and the respondents' attitudes towards consanguinity [6–11].

There is a long tradition of consanguineous marriage in many communities throughout the world, [9–12] especially in countries of the Middle East, Northern Africa and South Asia [4–9]. While the rate of consanguinity varies within the Middle East region, the difference is usually related to religion, race, ethnicity and sociocultural factors, including socially accepted norms of endogamy in tribal societies [1,2,4–18]. Among the major populations studied, the highest rates of consanguineous marriages have been associated with socioeconomic levels, illiteracy and rural residence [1,2,4,7–8]. Recent studies show that the prevalence of consanguineous marriages varies from 51–58% in Jordan [10], to 54% in Kuwait [4], 49% to 33% in Tunisia and Morocco [12], 58% in Saudi Arabia [13], 50% in United Arab Emirates [11], 52% in Qatar [1–2,14], 40–47% Yemen [16], 50% in Oman [18]. and as high as 68% in Alexandria, Egypt [19].

Genetic carrier screening programmes are systematic programmes, generally being recommended by government health bodies, advising the entire population of asymptomatic individuals of reproductive age to have a screening test to identify those who are carriers of autosomal recessive disorders. In some contexts, the screening programme may be recommended for subpopulations whose risk of particular genetic diseases is known to be increased [1–8]. These programmes are designed to determine whether individuals carry a genetic predisposition that may produce a disease in their offspring [2,3].

Several authors reported the common effect of inbreeding on health which focused mainly on its impact on reproduction, childhood mortality and rare Mendelian disorders [1,2,6,9,20–26]. Nevertheless, some limited information is available on the possible role of consanguinity and recessive genes in multi-factorial or polygenic common adult diseases [1,2,20–26], also known as the common, complex degenerative disorders. The aim of the study was to determine the extent and nature of consanguinity in the Qatari population and its effects on the common non-communicable diseases, especially susceptibility to a range of chronic, complex diseases.

2. Subjects and method

This is a cross-sectional based on survey conducted at the Primary Health Care (PHC) Centres and Hospitals in the State of Qatar. The survey was conducted among Qatari national and Arab women aged 18–40 years old.

The data was collected through a validated questionnaire [1,2] based on face-to-face interviews by physicians and qualified nurses using the local language and perviou. The nurses were aware of the Arabic culture and were able to assist the study participants if they were unable to answer the questions. Data collection took place from January 2013 to May 2014. The sample size was determined on the *a priori* presumption that the prevalence rate Premarital Screening and Genetic Counseling [PMSGC] in neighbouring countries would be similar to the rates found in other countries in the Arab Gulf Counties [1–8,11]. The reported prevalence of consanguinity in Arab and Middle-East Countries were vary between 35–40% with the 99% confidence interval for 3% error of estimation, a sample size of 1626 subjects would be required for this study to achieve objective. Of the 22 primary health care centres available, we selected 13 health centres on a random sampling basis. A multi-stage sampling design was used and a representative sample of 1626 women aged 18–45 years were approached and 1228 subjects agreed to participate (75.5%) and responded to the study. Furthermore, content validity, face validity and reliability of the questionnaire were tested in a sample of 100 subjects and demonstrated high levels of validity and a high degree of reliability (Kappa = 0.84); 72% and-reported diseases were confirmed in medical charts. All information was gathered based on structured face-to-face interviews by physicians and qualified nurses using the local language. The relationship between the spouses was recorded and whether their parents were consanguineous. Marriages between relatives were classified in six groups: double first cousins; first cousins; first cousin once removed; second cousin; less than second cousin (third cousin); and non-consanguineous marriage.

Odds ratios were computed for the likelihood of disease by consanguinity status in the current generation as well as the respondent's children. For the current generation, cases were defined as respondents who were an offspring of consanguineous unions (disease report limited to either self or siblings having the disease) and controls were defined as respondents who were an offspring of non-consanguineous unions (disease report limited to either them-self or siblings having the disease).Similarly definitions were adopted for responder's offspring. Chi-square test was used to ascertain the association between two or more categorical variables. In 2×2 tables, the Fisher exact test (two-tailed) was used when the sample size was small. Relative risk and 95% confidence interval were calculated using Mantel-Haenszel method. All statistical tests were two-sided and $P < 0.05$ was considered statistically significant.

3. Results

The mean age ± S.D of the 1228 women interviewed was 39.25 ± 9.57 years. The rate of consanguinity in the present generation was 43.5% [95% CI = 47.7–54.4]. The socio-demographic characteristics of consanguineous and non-consanguineous distribution in the study population is shown in Table 1. There were statistically significant differences between consanguineous and non-consanguineous participants with regards to age, educational status, occupation status, household income. BMI, cigarette smoking and sheesha smoking. Although a similar pattern between consanguinity and husband's education was observed, the differences were smaller and not statistically significant. Table 2, give some characteristics of studied subjects according to life-style habits, No. of parity, number of gravid and number of children are alive.

Data on trends in levels of consanguinity in the current generation compared to the parental generation and the associated coefficient of inbreeding are presented in Table 3. The most common type of consanguineous marriage was first cousin marriage (284, 23.1%). The second most common category of consanguineous marriages was double first cousin marriages (41, 3.3%). The coefficient of inbreeding in the respondent, husband's parents and respondent's parents were 0.017591, 0.018738 and 0.06794 and, respectively. All types of consanguineous marriages were higher in the respondent's generation, particularly first cousin (23.1% versus 22.1% paternal and 21.3% maternal) and double first cousins (3.2% versus 3.1% paternal and 2.9% maternal).

Table 1
The socio-demographic of studied subjects by consanguinity (N = 1228).

Variable	Consanguineous (N = 534) n (%)	Non-Consanguineous (N = 694) n (%)	p value
Age in Years			
<25 years old	53(9.9)	65 (9.4)	
25–34 years old	138 (29.8)	198 (51.7)	
34–44 years old	197 (36.9)	245 (51.7)	0.768
⩾45 years old	146 (27.3)	186 (48.3)	
Mother education			
Illiterate	41 (7.7)	65 (9.4)	
Elementary	73 (13.7)	75 (10.8)	
Intermediate	119 (22.3)	109(15.7)	0.010
Secondary	165(30.9)	235 (33.9)	
University	136 (25.5)	210 (30.3)	
Mother occupation			
Sedentary Professional	37 (6.9)	65 (9.4)	
Teacher	146 (27.3)	234 (33.7)	
Businessman	18 (3.4)	32 (4.6)	0.009
Arm/Police	22 (4.1)	18 (2.6)	
Housewife	311 (58.2)	345 (49.7)	
Father education			
Illiterate	19 (3.6)	34 (4.9)	
Elementary	61 (11.4)	40 (5.8)	
Intermediate	106 (19.9)	92(13.3)	<0.001
Secondary	207(38.8)	286 (41.2)	
University	141 (26.4)	242 (34.9)	
Father occupation			
Sedentary Professional	144 (27.0)	182 (26.2)	
Clerk/Officer	223 (41.8)	251 (36.2)	
Businessman	44 (8.2)	120 (17.3)	<0.001
Arm/Police	86 (16.1)	90 (13.0)	
Student	37 (6.9)	51 (7.3)	
Household Income			
<$1500 US Dollars	40 (7.5)	60 (8.6)	
$1500-$3499	165 (30.9)	182 (26.2)	
$3500-$5499	108 (20.0)	171 (24.6)	<0.001
$5500-$7499	145 (27.2)	181 (26.1)	
⩾$7500	76 (14.2)	100 (14.4)	
Place of Living			
Urban	404 (75.7)	572 (82.4)	0.004
Semi-Urban	130 (24.3)	122 (17.6)	

Table 2
Some characteristics of studied subjects according to life-style habits, No. of parity, number of gravid and number of children are alive (N = 1228).

Variable	Consanguineous (N = 534) n (%)	Non-Consanguineous (N = 694) n (%)	p
Age in Years			
Mean ± St. Deviation	4.76 ± 2.00	4.79 ± 2.05	0.843
Cigarette smokers			
Yes	35(6.6)	73 (10.5)	0.015
No	499 (93.4)	621 (89.5)	
Sheesha (Water-pipe) smokers			
Yes	58 (10.9)	104 (15.0)	0.034
No	476 (89.1)	590 (85.0)	
BMI			
Normal (<25 kg/m^2)	174 (32.6)	273 (39.3)	
Overweight (25–30 kg/m^2)	210 (39.3)	253 (36.5)	0.045
Obese (30 + kg/m^2)	150 (28.1)	168 (24.2)	
No. of bedrooms at home			
Mean ± St. Deviation	4.76 ± 2.00	4.79 ± 2.05	0.843
No. of peoples at home			
Mean ± St. Deviation	5.72 ± 2.26	5.98 ± 2.54	0.058
Parity number			
Mean ± St. Deviation	5.34 ± 2.93	5.80 ± 2.81	0.004
Gravid number			
Mean ± St. Deviation	6.20 ± 3.12	6.67 ± 3.17	0.011
No. of children are alive			
Mean ± St. Deviation	5.28 ± 2.93	5.67 ± 2.88	0.019

The prevalence of common adult diseases among parents and the current generation and their offspring by consanguineous [Table 4] showed that there was a statistically significant difference in the two groups, parents and the current generation, in relation to cancer, blood disorders, mental disorders, heart diseases, asthma, hypertension, hearing deficit G6PD and diabetes mellitus. There was also a significant difference in the prevalence between the offspring of consanguineous versus non-consanguineous for all cases: cancer, blood disorders, anemia, mental disorders, heart diseases, asthma, hypertension, gastrointestinal diseases, hearing deficits, common eye diseases and diabetes mellitus All reported diseases were more frequent in consanguineous marriages.

4. Discussion

Genetic screening programmes are often related to the stage of life when they are carried out. Worldwide, genetic screening programmes may be made available in pregnancy, in the newborn period, or in adolescence or early adult life before marriage or conception [1–15,16]. Those programmes conducted before birth, such as screening of foetal cells in maternal blood, maternal serum screening, and ultrasound screening, are designed to detect genetic disorders or malformation during early pregnancy, thus allowing couples to decide whether to terminate or continue the pregnancy. If a couple chooses to continue the pregnancy, the early diagnosis enables them and the healthcare provider to set a strategy for the child's treatment and follow-up [1,2–4,8].

The already well-defined impact of consanguinity on the incidence of autosomal recessive disorders being expressed in the progeny of a consanguineous union is not the prime focus of this study. The disease incidence is inversely proportional to the frequency of the disease allele in the total gene pool [5]. Many rare disease genes have been identified and their chromosomal locations mapped by studying highly inbred families with multiple affected members [25–30,31,32]. The main impact of inbreeding to be studied in the past has been the increase in the frequency of homozygotes for recessive disorders [6,19,27]. In an Eastern province of Saudi Arabia [33], the rate of consanguineous marriage was as high as 52.0% with an average inbreeding coefficient of 0.0312, slightly higher than that of the present study where the coefficients of inbreeding in the respondent, husband's parents and wife's parents are 0.017591, 0.018738 and 0.016794, respectively .

Some reports have indicated that there may be inconsistencies in counseling for consanguinity among health care providers [2,10]. It is important that primary health care providers, specifically in highly consanguineous communities, have clear evidence-based guidelines in counseling a consanguineous couple to minimize their risks for having affected offspring. Though some recessive alleles are beneficial in the heterozygote, the overall effects of inbreeding in wider communities help us to understand unfavourable medical outcomes. Epidemiological studies show a significant increase in the health burden of consanguinity, especially in developing countries in which religious and socioeconomic considerations favour intra-familial marriages. In Figs. 1 and 2 the prevalence of consanguinity is shown to be very high in the Asian and African countries as compared to Australia or Untied States of America [34,35]. In the Muslim populations of Asia mainly among Arabs and African countries, cousin marriage is often strictly followed.

Qatar is the last Gulf nation to institute carrier screening for genetic disorders but many nationals remain unaware of the risks of consanguineous marriages. These results indicate that more effort needs to be made to develop public health strategies to improve the population's understanding of the costs and benefits

Table 3
Consanguinity in current generation compared to parental generation.

Degree of consanguinity*	Current generation		Husband's parents		Wife's parents	
	n (%)	Inbreeding coefficient	n (%)	Inbreeding coefficient	n (%)	Inbreeding coefficient
No consanguinity	694 (56.5)		684 (55.7)		720 (58.6)	
Consanguinity	534 (43.5)		544 (44.3)		508 (41.4)	
Double first cousin	41 (3.3)	0.004125	40 (3.3)	0.004071	36 (2.9)	0.003625
First cousin (father's side uncle) Type I	196 (16.0)	0.014437	164 (13.4)	0.013792	167 (13.6)	0.013313
First cousin (mother's side aunt) Type II	25 (2.0)		41 (3.3)		28 (2.3)	
First cousin (mother's side uncle) Type III	36 (2.9)		21 (1.7)		29 (2.4)	
First cousin (Father's side aunt) Type IV	27 (2.2)		45 (3.7)		38 (3.1)	
Subtotal	284 (23.1)		271 (22.1)		262 (21.3)	
First cousins once removed	48 (3.9)	0.001212	34 (2.8)	0.000875	25 (2.0)	0.000636
Second cousin	31 (2.5)	0.000390	64 (5.2)	0.000814	34 (2.8)	0.000432
Less than second cousin	130 (10.6)		135 (11.0)		151 (12.3)	
Total coefficient of inbreeding*		0.017591		0.018738		0.016794

* Inbreeding coefficient up to 2nd cousins.

Table 4
Prevalence of common adult diseases among current generation and offspring by consanguineous and non consanguineous unions.

Current Generation	C = 508	NC = 720	OR and 95% CI	P value
Cancer	38	11	5.18(2.62–10.25)	<0.001
Blood Disorder	27	11	3.61(1.17–7.36)	<0.004
Anemia	37	17	3.25(1.80–5.83)	0.001
Mental Disorders	15	6	3.56(1.39–9.40)	0.008
Heart Diseases	46	24	2.89(1.73–4.79)	0.001
Bronchial Asthma	42	14	4.54(2.45–8.41)	<0.001
Gastrointestinal diseases	12	7	2.42(0.94–6.20)	0.069
Hypertension	38	16	3.55(1.96–6.45)	<0.001
Cerebrovascular / stroke	14	5	4.05(1.45–11.32)	<0.007
Hearing Deficit	23	12	2.79(1.37–5.68)	0.004
G6PD	26	14	2.70(1.40–5.26)	0.003
Diabetes Mellitus	46	24	2.88(1.73–4.79)	<0.001
Offspring	C (N = 534) n	NC (N = 694) n	OR and 95% CI	P value
Cancer	29	8	4.92(2.29–10.86)	<0.001
Blood Disorder	22	4	7.11(2.53–21.64)	<0.001
Anemia	55	32	2.37(1.51–3.73)	<0.001
Mental Disorders	8	4	2.62(0.78–8.75)	0.116
Heart Diseases	27	10	3.64(1.74–7.59)	<0.006
Bronchial Asthma	56	37	2.08(1.35–3.20)	0.009
Gastrointestinal diseases	22	13	2.21(1.10–4.44)	0.024
Hypertension	24	10	3.21(1.52–6.79)	0.003
Hearing Deficit	27	7	5.22(2.58–12.09)	<0.001
Low Birth Weight	17	4	5.67(1.62–8.34)	<0.001
Common eye diseases	22	8	3.68(1.62–8.34)	0.002
Diabetes Mellitus	54	15	5.09(2.84–9.13)	<0.001

Note. C: Consanguineous.
NC: Non Consanguineous.
OR = Odds Ratio and 95% Confidence Interval.

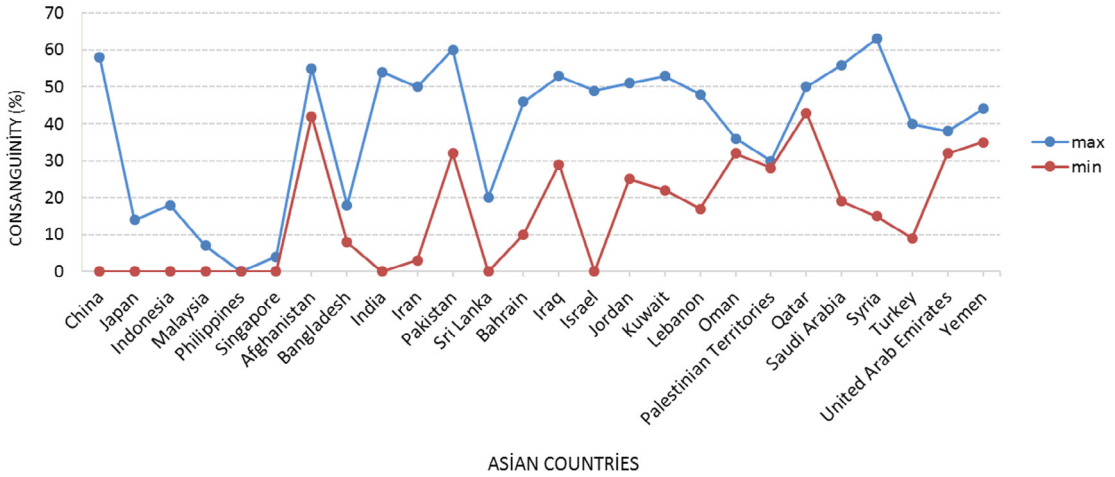

Fig. 1. The consanguinity rates among Asian countries with higher minimum and maximum levels shows that the populations of these countries strictly favour cousin marriages.

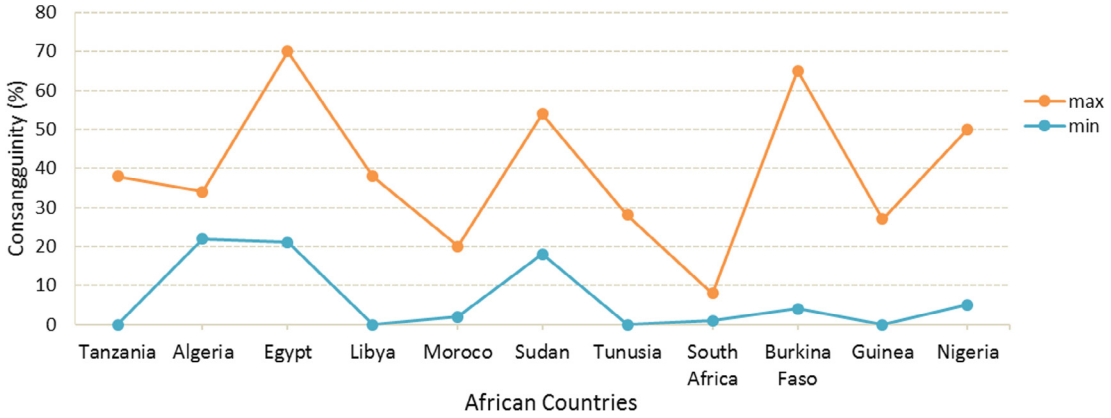

Fig. 2. The consanguinity rates among African countries with higher minimum and maximum levels shows that the populations of these countries strictly favour cousin marriages.

involved in contracting consanguineous marriages, given the goal of healthy offspring. Our data suggest that the increased incidence of he common, complex disorders is an additional factor to be considered as a disadvantage of consanguineous marriage, in addition to he increased risks of Mendelian recessive disorders. Finally, health authorities, health care providers, genetic consular or academicians could consider both the negative impact of consanguineous marriage in terms of increased genetic risks to the offspring, as opposed to the potential social cultural and economic benefits.

This study stresses on the importance of the genetically and hereditary screening program in state of Qatar. However, there are several limitations. First, this is a cross sectional study and, thereby, subjects might be misclassified in this analysis. Second, the study sample is based on PHC clinics visits. Third, the majority of the study sample was Arab women and of relatively high socioeconomic and education status; hence, results may not be generalizable to the population of all married subjects. Furthermore, it is worth noting that there might be some bias in data associated with the ages of participants and reporting of diseases such as cancer, hypertension, diabetes and coronary heart diseases, which may arise later in life (in both cases and controls). This cohort is also diverse in terms of geographic region of the country and race/ethnicity. Results must also be interpreted in the context of study limitations.

5. Conclusion

This current study showed a higher incidence of certain diseases in consanguineous couples and that in a population with a high rate of consanguinity, there is a significant increase in the prevalence of common adult diseases such as diabetes, cancer, blood disorders, mental disorders, heart diseases, asthma, gastrointestinal disorders, hypertension, hearing deficit, G6PD and common eye diseases.

6. Contributors

AB was involved in data collection, statistical analysis, interpretation of data and writing the manuscript. RM was involved in interpretation of data, writing and editing the manuscript. All authors approved the final version.

Ethics committee approval

Ethics committee approval was received for this study.

Informed consent

Informed consent was obtained for this study.

Compliance with ethical standard

This article does not contain any studies with human participants or animals performed by any of the authors.

Financial disclosure

The authors declared that this study has received no financial support.

Competing interests

We have no financial interest to declare.

Acknowledgement

The authors would like to thank the Hamad Medical Corporation – Translational Research Institute and Primary Health Corporation for their support and ethical approval (HMC RC#12240/12). They would also like to thank Prof Angus Clarke of Cardiff University (Wales, UK) for comments on a draft of the manuscript.

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