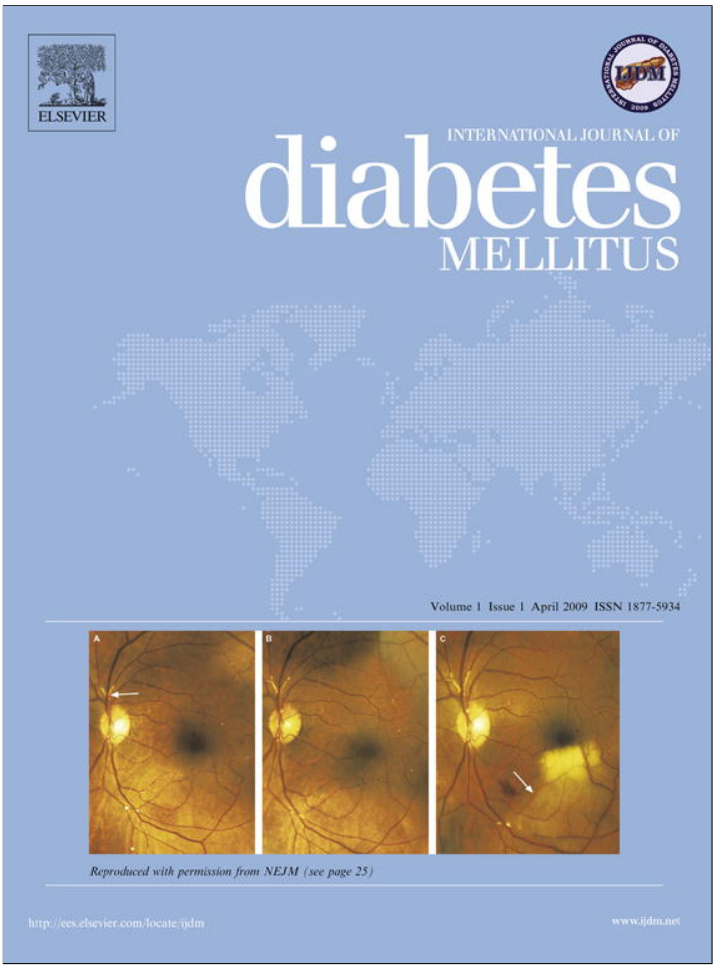
Obesity, diabetes and longevity in the Gulf: is there a Gulf Metabolic Syndrome?



International Journal of Diabetes Mellitus 1 (2009) 43–54

Contents lists available at ScienceDirect

International Journal of Diabetes Mellitus

journal homepage: ees.elsevier.com/locate/ijdm

Special Commentary

Obesity, diabetes and longevity in the Gulf: Is there a Gulf Metabolic Syndrome?☆

"....we do not always bear in mind, that though food may be now superabundant, it is not so at all seasons of each recurring year"
***Charles Darwin* (The Origin of Species)**

1. Introduction

The above quote in the year of Darwin's 200th birthday is highly poignant as modern humans inextricably move towards a lifestyle-induced pandemic, with rampant levels of obesity, type 2 diabetes mellitus (T2DM) and insulin resistance [1]. Unfortunately, the Gulf appears to be leading the world, with T2DM rates reaching 35% in some populations [2].

There appear to be two main causes. The first is that humans, like most animals, are inherently thrifty (epitomised by insulin resistance). Life evolved in a famine and feast environment, which has resulted in 'thriftiness' becoming a genetically canalised trait resistant to mutational perturbation. However, expression of this phenotype can be epigenetically modulated both through the *in utero* environment and that of the preceding 2–3 generations [3]. The second is that this epigenetic canalisation is likely modulated by hormetic stress factors, such as exercise, fasting, temperature extremes and even dietary factors. These induce mild physiological oxidative stress, which results in mitochondrial biogenesis and an increased anti-oxidant capacity. Without these, mitochondrially-dependent metabolic flexibility can be lost, leading to a condition currently known as the 'metabolic syndrome' [4]. Hormesis is well described to extend life span in several model organisms [5]; in essence, hormesis is the process where a small stress increases resistance to that stress, so improving overall biological fitness. The underlying process may be represented by 'redox-thriftiness', where insulin resistance is determined by the ability to resist oxidative stress. Without hormetic stimulus, metabolic flexibility and resistance to oxidative stress is reduced, resulting in heightened insulin resistance. This could potentially lead, in a calorie rich environment, to a tipping point where physiological insulin resistance becomes pathological due to rising oxidative stress and inflammation driven by ectopic fat deposition, which results in accelerated ageing [6].

It is well established that as body mass index (BMI) increases, so does oxidative stress, which is worsened if T2DM develops – further reducing life expectancy [7–9]. In fact, the metabolic syndrome is associated with an earlier than normal onset of many diseases of ageing, including renal disease, cancer, osteoporosis, depression and neurodegeneration, as well as loss of sexual function and fertility [10–15]. Of particular relevance may be polycystic ovary syndrome (PCOS); central obesity and insulin resistance, and thus, the metabolic syndrome may play a very important role in its aetiology. Certainly, a better lifestyle, as well as the insulin sensitiser, metformin, are key in its treatment [16]. There is no published data on its prevalence in the Gulf. It is therefore important to consider the metabolic syndrome not as an all or nothing condition, but as a continuum with its roots very early in life, even *in utero*, which can be programmed by maternal high calorie diets [17].

It is therefore likely that T2DM is just the tip of a Gulf Metabolic Syndrome iceberg. The metabolic syndrome is currently defined as central obesity plus two of the following factors: raised triglycerides (TGs), reduced HDL, hypertension and evidence of pathological insulin resistance, such as raised fasting plasma glucose (FPG, now defined as >5.6 mM) or previous T2DM [18]. However, the current definitions have evolved from insulin resistance- to waist measurement-centric, and still give widely differing prevalences [19], suggesting that truncal fat-based definitions need to evolve further, as there are significant differences between ethnic groups as well as gender [20]. For instance, current metabolic syndrome definitions often miss slim individuals who may still be at high risk of cardiovascular disease [21]. This indicates that more accurate assessment of internal ectopic fat will be necessary as an early marker of metabolic inflexibility, for example, by *in vivo* imaging.

Implicit in this is that current definitions may seriously under estimate the true extent of this condition: it is plausible that in a region where the population is still very young, and 1 in 2 people are *clinically* obese, with over a third having diagnosed T2DM, symptoms of the metabolic syndrome may be present in the great majority. Clearly, the term 'metabolic syndrome' is not descriptive of the condition now afflicting a large fraction the Gulf. We have previously proposed that a more appropriate term might be the '***L****ifestyle-****I****nduced* ***M****etabolic* ***I****nflexibili****T****y and accelerated* ***AGE****ing*', or, 'LIMIT-AGE' syndrome [6].

In this paper, we suggest that the Gulf Metabolic Syndrome represents an extreme example of a lifestyle-induced problem brought about by the rapidity of oil wealth-induced 'obesogenic urbanisation'. For instance, the society-wide introduction and availability of labour saving devices, cheap high calorie food, freely available water, as well as air conditioning. This has resulted in the removal of nearly all positive hormetic stressors that have, in the past, optimised biological fitness of the population and has occurred in an extremely short and epigenetically important time frame of 2–3 generations. This may be resulting in direct epigenetic transfer of metabolic inflexibility between generations. Although other cultures have experienced increased wealth, it has been over a much longer period, and critically, has allowed society to adapt. For instance, in Brazil, obesity was initially a problem of the higher socio-economic groups, but as

☆ Dr. Geoffrey Guy and Dr. Alistair Nunn are equal co-authors and contributors. The manuscript was written by Dr. Alistair Nunn, with additional data supplied by Dr. Louise Thomas and Professor Jimmy Bell.

1877-5934/$ - see front matter
doi:10.1016/j.ijdm.2009.05.001

wealth spread (indicated by increasing urbanisation and the generation of an obesogenic environment), it shifted to the poorer socioeconomic groups, while the better off started to become thinner again. Over a 28 year period (1975 to 2003), the overall obesity rate in Brazil rose from about 5.0% to 11.3% [22]. Using combined data for Saudi [23–25], linear extrapolation would suggest that prevalence rate for obesity rose from less than 5% to more than 40% over the same period. Perhaps the most startling statistic is that obesity rates in Saudi school boys have risen from 3.4% in 1988 to 23.4% in 2005 [26]. Another example of this compression of wealth distribution into a short time period might also explain why the Hispanics in the US have a higher rate of obesity and diabetes than the African American [7], as the latter have had time to adapt to the US lifestyle (they have been exposed for many generations, whereas Hispanic immigration is only 2–3 generations old). The ultimate conclusion is that within this generation, some Gulf populations may start to experience significant falls in absolute life expectancy, while their healthy life expectancy could fall to less than 40 years. As the metabolic syndrome is largely preventable, a return to a healthier way of living is of paramount importance in this region – in all age groups. It may well be less about genetics (given that all humans are thrifty), but more about epigenetics and breaking the transmission of stress-induced insulin resistance between generations by reinstatement of hormesis.

2. The obesity & T2DM pandemic in the Gulf and Saudi Arabia

Prevalence rates for T2DM and CVD in sub-Saharan Africa have seen a 10-fold increase in the last 20 years. In the Arab Gulf current prevalence rates are between 25% and 35% for the adult population, whilst evidence of the metabolic syndrome is emerging in children and adolescents [2]. A recent International Diabetes Federation (IDF) summary suggests that countries in the Gulf region have some of the highest rates of T2DM in the world (Fig. 1): this is likely to be an underestimate.

2.1. Obesity

One of the strongest associations with T2DM is obesity, and the resulting condition is often called 'diabesity'. The Gulf region not only has some of the highest rates in the world, but the rate of increase has been dramatically faster than most other countries. Fig. 2 shows a composite of obesity prevalence data from Kuwait, Saudi Arabia and Bahrain, compared with the global rates, and those of USA and Brazil [22–31]. The main thing to note is the slope of the plotted lines: prevalence rates of obesity in Kuwait and Saudi Arabia could approach 70% by 2020. The data also show the variability between the sexes in different countries.

		Estimated diabetes prevalence	
Position	**Country**	**2007**	**2025**
1	Nauru	30.7	32.3
2	United Arab Emirates	19.5	21.9
3	Saudi Arabia	16.7	18.4
4	Bahrain	15.2	17.0
5	Kuwait	14.4	16.4
6	Oman	13.1	15.2
7	Tonga	12.9	14.7
8	Mauritius	11.1	13.4
9	Egypt	11.0	13.4
10	Mexico	10.6	12.4

Adapted from Diabetes Atlas, 3rd Edition, 2006, International Diabetes Federation

Fig. 1. Recent IDF league table of diabetes rates.

A recent study undertaken in 2006 in Saudi Arabia suggests that only 19.9% of Saudis attending primary health care clinics had a normal body weight: 49.9% were obese [32]. This has risen from a rate of 35.6% in the late 1990s [33]. Worryingly, it is occurring in a younger and younger population; in Saudi pre-school children, it was estimated to be 10.8% in 2006 [34]. The rate in Kuwait adolescents was already exceeding that of the United States in 2002 (19.9% vs 15.3%) [35,36]. Clearly a significant number of people in the Gulf are overweight – and getting fatter: the mean BMI in Saudi Arabia in the late 1990s was about 29 kg/m^2 [24]; using data from 2006 [37], the mean BMI was about 30.8 kg/m^2. In comparison, in Kuwait in 2005/6, the mean BMI was 29 kg/m^2, with nearly half of Kuwaitis having a BMI 30 kg/m^2 or greater [38].

2.2. The metabolic syndrome

Although the genetics background associated with the metabolic syndrome is not fully understood, a recent study found a high prevalence of a mutation that reduced insulin secretion in Saudi Arabia [39]. In the late 1990s, Saudi Arabia had a rate of 39.3%, with greater rates found in females (42 versus 37.2% for men) and in urban, compared to rural populations (44.1 versus 35.6%, respectively) [40]. Fig. 3 shows that the prevalence of the metabolic syndrome rises rapidly with age [40–44]. As many countries in the Gulf, such as Kuwait, have relative young societies (in the early 1980s, nearly half the population were under 15) [45], then it is possible that as many as 1 in 2 Kuwaitis may have definable metabolic syndrome by 2020. As Fig. 3 suggests, it is already likely that Saudi Arabia may have a rate of 1 in 2. Left untreated, many of these people may well go on to develop T2DM.

2.3. Type 2 diabetes mellitus

The rising levels of obesity and the metabolic syndrome are leading to a pandemic of diseases, in particular T2DM. However, it is difficult to precisely define and compare the prevalence, as the rates are often measured in different age groups, as well as in different areas – and so may not always be representative of the population. Moreover, they are often measured over a period of time. However, some estimates suggest that in the early part of the new millennium the rates in the Saudi population were between 25% and 30%, 3% in the Sudan, 35% in Bahrain, 21% in Oman, and about 17% in Kuwait [46].

One very important aspect is to ascertain the rate of increase. In a comprehensive study in Saudi Arabia in the early 1990s, the rates were 5.5% and 4.6% (2–70 years age group, male/female) and 9.5% and 6.8% (14–70 years age group, male/female). Above 30 years, these rates rose to 17.3% and 12.2%, respectively [47]. In the late 1990s in Saudi Arabia, another large scale representative study of 30–70 year olds suggested a prevalence of 23.7%, with a higher rate in males compared to females (26.2% versus 23.7%, respectively), and a higher prevalence in urban versus rural areas (25.5% versus 19.5%, respectively) [33]. It appears that the rate is increasing much faster in Saudi Arabia compared to other countries, although it is still less than Bahrain.

However, it is becoming apparent that T2DM rates are often underestimated. The 2007 estimate of T2DM in Kuwait, suggested a rate of 16.7%. However, the rate in 1995 was already about 14.8% [48]. One of the emerging problems in assessing the prevalence of T2DM is that much goes un-detected: Saadi et al. have recently found that the original headline diabetic rate in Al Ain in the United Arab Emirates (UAE) was thought to be about 10%, however,

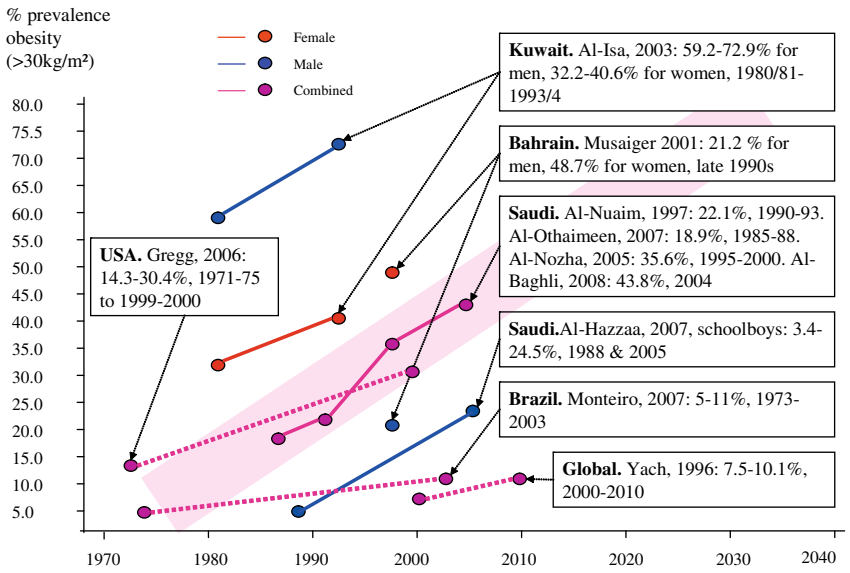


Fig. 2. Rates of obesity in the Gulf compared to other countries. Gulf countries solid lines, non-Gulf countries depicted using broken lines. The shaded band represents a linear prediction.

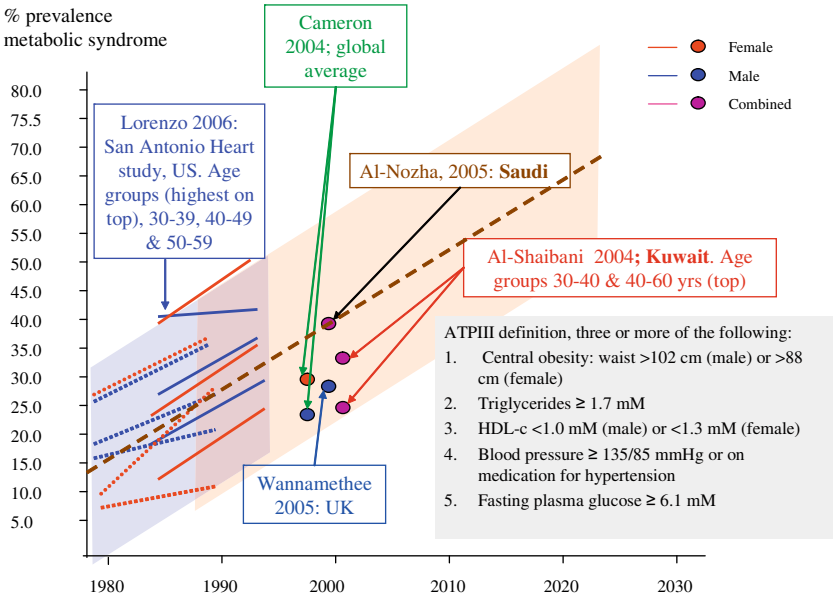


Fig. 3. Prevalence of the metabolic syndrome globally and in the Gulf.

more detailed analysis and investigation suggested an age-adjusted rate of nearer 29% [49].

Because of these uncertainties, we resorted to using established odds ratios (OR) and life time risk of developing T2DM based on BMI. In a retrospective analysis of more than 123,000 US healthcare workers, Field et al. determined the 10 year risk of developing T2DM in different BMI categories. Within a BMI range of 30–34.9 kg/m^2, the OR for women was 10.0 and 11.2 for men, reaching 17.0 and 23.4, respectively, when over 35 kg/m^2 [50]. In a more recent analysis, Narayan and colleagues calculated the lifetime BMI-associated risk of developing T2DM from data involving over 780,000 US subjects: lifetime T2DM risk at 18 years of age was found to increase from 7.6% to 70.3% between underweight and very obese men and from 12.2% to 74.4% for women. This risk varied according to ethnic background. For instance, the lifetime risk of T2DM for subjects who are obese at 18 (BMI 30 to <35 kg/m^2) is 51.8% (male) and 48.8% (female) for non-Hispanic white subjects, rising to 68.1% (male) and 66% for Hispanics. At BMI's of greater than 35 kg/m^2, this rises to 66.1% and 69.3%, and 81.1% and 86.0%, respectively. Even at a baseline age of 45 years, with a BMI 30 to <35 kg/m^2, the figures are 47.5% and 42.2%, and 62.9% and 56.4%, respectively [7].

Using a 1995 Kuwait measured diabetic rate of 14.7%, a population of 2 million and an obesity rate of 40%, with an estimated normal weight diabetic rate of 1–3%, the 2005 calculated diabetic rate could have been between 21.4% and 34.6% – an average of 28%. An 18 year old cohort from 1995 would reach 60 years of age in 2037 and could have a diabetic rate of between 36–55%. Applying this calculation to 2007, the diabetic rate might have

been nearer 29% – suggesting that the current estimate of about 17% could be too low. With an obesity rate of 50% and a population of 2.6 million, an 18 year old 2007 cohort (where the median age was 26) would reach their 60th year in 2049: their diabetic rate could range between 38–53%. Which ever figures are used, it is clear that the Gulf is heading for a severe T2DM pandemic that could reach as high as 1 in 2 people in some countries. This data is supported by the predicted increases in obesity and metabolic syndrome.

3. Decreasing absolute and healthy life expectancy in the Gulf

Although average life expectancy has increased over the last 100 years to nearer 80 years in developed countries, there is clear evidence that it may have stopped rising and may even be decreasing. Moreover, it appears that the healthy life expectancy (the amount of chronic disease free life), has not kept pace with the increase in life expectancy. One likely explanation is that diseases associated with excessive fat deposition are now being treated, such as hyperlipidaemia and hypertension, but not cured. However, tellingly, T2DM is still on the increase. This has resulted in many people living for many years with chronic diseases in later life. The fundamental reason may have its roots deep in evolution and be related to hormesis, which suggests that the cause of the metabolic syndrome is largely environmental: both exercise and a healthy diet reduce pathological oxidative stress and protect against it [51,52]. One very important component is how excessive fat is handled, and in particular, how it is stored – fat in the wrong places can be highly inflammatory, but this may induce a mechanism to prevent excessive weight gain. However, this mechanism may also accelerate ageing; to help understand the relations between ectopic fat, visceral adipose tissue (VAT), insulin resistance and accelerated ageing, we have developed the concept of 'redox-thriftiness' [6].

3.1. Ectopic fat deposition and VAT: location, location, location

It has been suggested that a failure of fat cell proliferation, mitochondrial function and fat oxidation results in ectopic fat storage, insulin resistance and T2DM [53]. The metabolic syndrome may therefore be caused by lipid overflow into normally non-adipotic tissues, such as the liver, muscle, pancreas and heart, and is probably a combination of over-delivery and an inability to metabolise the fat that results in oxidative stress and inflammation [54]. Part of the problem is the chronic and continual exposure to high levels of lipids, as although high fat feeding can initially result in mitochondrial biogenesis in muscle and a degree of protective compensation, this effect can be lost during chronic high fat feeding [55]. However, it is not just excessive lipid within non-adipose cells that is lipotoxic; the presence of overloaded adipocytes in or near a particular organ can also negatively influence its function by localised release of cytokines. For instance, fat deposited around the heart, or even the aorta, is associated with vessel calcification [56]. One critical set of transcription factors involved in controlling potential lipid overload may be the PPARs. We have proposed they could be critical in preventing lipotoxicity by ensuring safe fat storage and burning – and thus playing a critical role in functional longevity. Suppression of PPAR activity (e.g. by inflammation) may play a critical role in a tipping point when normal physiological insulin resistance becomes pathological due to inflammation (see next section) [57].

The best recognised marker of the metabolic syndrome is excessive VAT. However, its role in the metabolic syndrome is still unclear: expansion of this depot may even initially have a protective function, suggesting individual capacity thresholds [58]. In support of this, we have proposed that the raised levels of endocannabinoids found in the metabolic syndrome may actually be a protective mechanism – especially in the visceral region, as they may have anti-inflammatory and adipogenic functions [59]. For instance, activation of PPAR γ enhances lipid trapping in subcutaneous adipose tissue (SCAT), but appears to both enhance lipolysis and fat burning in VAT, as well as inducing mitochondrial biogenesis in both tissues [60]. However, VAT may contain a higher density of mitochondria than SCAT, and has a higher oxidative capacity [61]. Hence, the finding that VAT exhibits a greater degree post-prandial thermogenesis, compared to SCAT, does suggest it is metabolically much more active [62]. We have therefore suggested that VAT could play an important role in preventing excessive fat deposition – this may be partly driven by inflammation [6].

In summary, mitochondrial dysfunction is an important cause of metabolic inflexibility and the metabolic syndrome [4]; it is thus likely that this inflexibility extends beyond muscle to just about every tissue – including adipose tissue. Within this paradigm, the expansion of VAT may be an inflammatory-driven short-term anti-lipotoxic mechanism – where the inflammation is derived from ectopic fat deposition. Thus, where the excess fat is deposited is critical.

3.2. Redox-thriftiness and hormetic stimuli

Thriftiness arose from an evolutionarily-driven need to minimise energy expenditure, which might reduce mitochondrial density [63]. However, this has to be balanced with the need to resist the oxidative stress associated with redox signalling and pathogen resistance. Redox signalling is a fundamental signalling mechanism [64,65] and the mitochondrion is critical [66]. This may have given rise to something we have called 'redox-thriftiness' [6]. In essence, mitochondria may be able to both amplify membrane-derived redox growth signals, but then negatively regulate them in concert with increased anti-oxidative stress systems, resulting in an increased ATP/ROS ratio. This means that the ability to resist oxidative stress may determine insulin resistance, as insulin signalling involves redox. In this paradigm we suggest that insulin initially induces mild oxidative stress (via membrane ROS, which is then amplified by the mitochondrion). The increased oxidative stress then suppresses the insulin signalling pathway (classic negative feedback). Hence, redox-thriftiness initially leads to physiological insulin resistance, which has the effect of both protecting the individual cell from excessive growth/inflammatory stress, while ensuring energy is channelled to the brain, the immune system, and for storage. However, the increased oxidative stress might act as a mild mitochondrial biogenic signal. The resultant improvement in mitochondrial function then reduces mitochondrial redox amplification of the insulin signal, maintaining insulin sensitivity. It is thus possible that optimum modulation of redox-thriftiness requires more than one 'mitohormetic' signal, for instance, concurrent insulin and environmental hormetic signals that stimulate mitochondrial biogenesis and resistance to oxidative stress.

This suggests that without enough hormetic stimuli, insulin resistance would increase – this was probably never the case in our ancestor's time. Indeed, life probably evolved in a 'hormetic zone' where a degree of stress results in optimal fitness [67]. 'Mitohormetic' stimuli that result in mitochondrial biogenesis, such as some plant polyphenols, cold, exercise and fasting, are protective and result in improved functional longevity [68]. The tipping point may well be determined by a combination of epigenetic factors and hormetic tone [59]. It is very likely that most individuals can become more thrifty, especially if they, or their immediate ancestors were exposed to famine – a thrifty 'epigenotype' [3]. A loss of hormetic tone, which is normally generated by physical activity,

fasting, temperature extremes, dehydration, or even dietary components (e.g. resveratrol), may result in a reduced ability to deal with excessive calories.

3.3. The tipping point, VAT and longevity

At the present time, definitions of the metabolic syndrome revolve around truncal fat and do not discriminate between internal and external abdominal fat, or other sites of ectopic fat deposition, such as the liver. However, it is clear that increased VAT is a major marker of risk, and does influence the pathology; recent data suggest that removal of VAT can increase life expectancy [69]. We have proposed that increasing visceral and ectopic fat drives a mild inflammatory response that may have two evolutionary functions: to prevent excessive weight gain, and to improve population turnover by shortening life expectancy (so is opposite to the longevity induced by calorie restriction) [6]. Fig. 4 summarises the tipping point and the role of hormesis (e.g. physical activity), and VAT, in determining healthy life expectancy. In essence, without hormetic stimuli, metabolic flexibility and the ability to resist a high intake of calories decreases. In a high calorie environment without hormesis, fat is not stored as efficiently, resulting in spill over into other organs, resulting in inflammation. One of the emergency stores could be VAT, which as it fills up, both attempts to burn off excessive energy while releasing an inflammatory anorexic signal, which increases insulin resistance. This results in what might be described as pathological insulin resistance, which is in fact a mechanism to prevent excessive weight gain. The downside, at least for the individual, is a rise in life shortening systemic oxidative stress. However, a powerful hormetic stimulus increases metabolic flexibility, which breaks the cycle, and enables the system to deal with more calories – even if it means storing excess energy.

3.4. Modern life expectancy

Average life expectancy from birth has increased steadily in the last 1000 years, and between 1900–1990 in developed countries, it rose from between 33–53 years (Portugal/Australia) to between 68–76 years (Poland/Japan) for men, and between 35–55 years (Portugal/Denmark) to 75–82 years (Hungary/Japan) for women [70]. The underlying improvements came from better hygiene and anti-pathogenic treatments, as well as better nutrition. The cause of death therefore shifted from infectious/parasitic diseases to chronic diseases related to 'ageing'. This then led to a great deal of excitement that the upper limit would continue to increase, rising to an average life expectancy of nearer 100 years by 2060 [71]. In fact, recent projections, based on cumulative damage to vascular elastin, suggest that the real upper limit may be nearer to 120 years [72].

Data now show that the projected increase in life expectancy in some countries, like the USA, has now reached a plateau and may even be falling. In the late 1990s, a female in the USA could expect to have another 18–20 years of life at age 65: in the coming decades, because of obesity, this could fall by several years [71]. This situation has been confused despite the fact that the average BMI and rate of obesity has risen rapidly (in the 25 years, obesity rates in adults have risen from 13% to 31% in the USA), because there has been a profound reduction in common cardiovascular risk factors due to drug treatments for hypercholesterolaemia and hypertension, as well as a reduction in smoking. However, T2DM has increased. The net result is a population that is, paradoxically, more obese, diabetic, arthritic, disabled, and medicated, but with lower overall CVD risk [29]. In short, despite lifestyle-induced chronic disease, people are surviving longer because of better healthcare – but are doing so with many co-morbidities.

This has led to the concept of healthy or successful aging and healthy life expectancy, as opposed to outright life expectancy. It is also called health-adjusted life expectancy (HALE). In essence, it is the period people can expect to live without poor health. In 2002, an African male could expect 40 years, while females in developed countries could expect 70 years [73]. Analysis of US data up to the 1990s by Robine and Ritchie [74] suggested that the increase in life expectancy was not matched by increased healthy life expectancy. In terms of mortality, the main culprits were disorders of the circulatory system, malignant neoplasms and accidents. In contrast, for morbidity, the ranking is still dis-

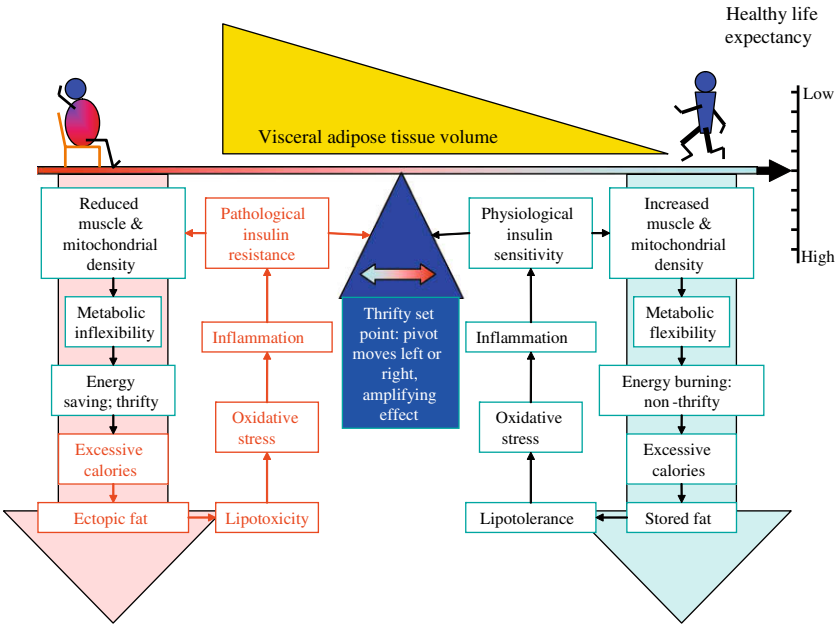


Fig. 4. Tipping point, hormesis, VAT and healthy life expectancy.

orders of the circulatory system, but then locomotor disorders and then respiratory disorders. In 1980, the life expectancy of the average man in the USA was about 79 years, but would expect to experience disability for the last seven years. For women, these figures were 83, and nine years, respectively. Using data in this paper, if the top four diseases were significantly reduced, an extra 11.6 years (average for both sexes) of disability free life could be added, plus another 6.5 years of life expectancy – a total of about 18.3 years. Thus, life expectancy could be increased to nearer 95–98 years, with only potentially 6–8 years of low-level disability at the end of life. Others have concluded that in the modern (developed) world, a long life is not necessarily a healthy one [75].

In summary, although the average life expectancy for most people in the developed world is about 80 years, they are experiencing increased morbidity and reduced quality of life in later years. If only circulatory diseases could be reduced, then an extra 4.2 years of disease free life could be expected, with another 4.1 years of life expectancy – a gain of 8.3 years [74]. Critically, many of the factors that lead to circulatory disease are modifiable and thus largely preventable to some degree. The best way to do this is via a proper lifestyle, involving both good nutrition and a reasonable level of physical activity [76,77].

3.5. Healthy and absolute life expectancy in the Gulf

The preceding discussion suggests a spiralling level of morbidity in the Gulf. BMI-related risk can start to increase at 25 kg/m^2 or even less. For instance, risk of CHD can rise by 8% per BMI point [78], while a BMI of 40 kg/m^2 or more is associated with a 52% greater chance of dying for cancer for men, and 62% for women [79]. Data show that if someone maintains a BMI of about 35 throughout their life (from 20 years of age), then they can expect to live 2–4 years less than average, falling by 4–6 years as their BMI reaches 40 kg/m^2 [80]. However, other estimates suggest that being obese at the age of 40 reduces lifespan by as much as seven years, while even having a BMI of 25 kg/m^2 may reduce it by two [81]. However, these effects on life expectancy are drastically modified by T2DM [7]. In contrast, it is possible to be overweight, but fit and insulin sensitive without the metabolic syndrome; this phenotype could be represented by a swimmer, a body builder or even a Sumo wrestler. It is thus vital to understand that the negative connotations of an above average BMI must be taken in the context of the person's lifestyle.

The risk of T2DM is on par with the risk associated with moderate smoking, with one estimate suggesting it reduces life expectancy by as much as 10 years [81]. It has been calculated that in the year 2000, in individuals with T2DM younger than 35 years, 75% of all deaths were attributable to T2DM. In individuals with T2DM aged 35–64 years, 59% of deaths were attributable to T2DM; while individuals with T2DM and older than 64 years, 29% of all deaths were attributable to T2DM [82]. Narayan and colleagues calculated that if someone had a BMI of 30–35 kg/m^2 at age 18 years, developing T2DM could reduce life expectancy by as much as 10–12 years. Life expectancy could fall by as much as 15 or so years if the BMI was greater than 35 kg/m^2. As expected, the effect on life expectancy reduced with advancing age of onset [7]. Interestingly, if these overweight subjects did not develop T2DM, they could expect a relatively normal lifespan [7] – which reinforces the importance of T2DM as a major risk factor.

The very high rates of obesity and emerging T2DM in the Gulf could have a serious impact on life expectancy. Using the above data, with a median age of 26 in 2007, an obesity rate of 50%, a metabolic syndrome rate approaching 40%, and possibly, a diabetic rate approaching 30%, then at least 30–40% of those alive in 2007 may have their life expectancy reduced from approximately 76–79 to 64–67 years. However, if the obesity rates continue to rise at the predicted rate (and the population still retain a non-hormetic lifestyle), resulting in an expansion of the cohort with a BMI of greater than 35 kg/m^2, then a percentage (as much 10%), may see their life expectancy reduced to less than 60 years of age, with a healthy life expectancy of not much more than 40 years. This may be 30–40 years less than what may be achievable.

4. Why the Gulf Metabolic Syndrome is so severe

The main reason is likely due to a rapid removal of hormetic stimuli in a very short time period, and the sudden presence of unlimited calories. Countries who have had their wealth the longest, such as Saudi Arabia, could be worst affected. Furthermore, this change has happened within epigenetic memory of harder times (i.e., a few generations). The result is that a thrifty epigenotype adapted to a harder environment, but normally exposed to

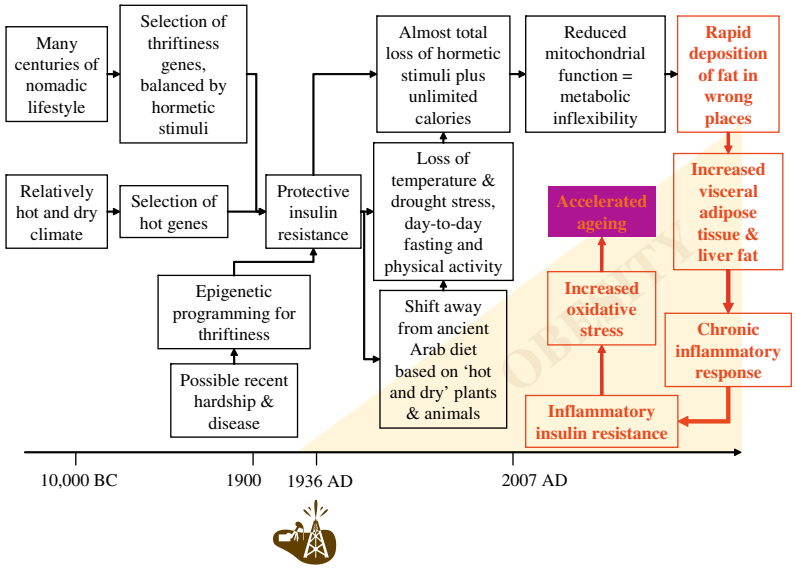


Fig. 5. Loss of hormesis in the Gulf environment.

hormetic stimuli, has been plunged into an environment for which it is not adapted. Fig. 5 summarises the problem.

4.1. Obesogenic urbanisation – shifting away from a hormetic environment?

Arabia was originally a land of great fertility, however, over thousands of years, it has been drying out and losing cultivable land. The current climate is now extremely warm and dry, which has resulted in a way of life adapted to these conditions, including the diet and use of drought resistance and hardy animals. It is therefore likely that the epigenotype of indigenous populations became adapted to hormetic factors, such as heat stress, physical activity (travel), periods of fasting (famine), dehydration and polyphenolic compounds from stress resistant plants (both directly, and indirectly through animals, such as camels or goats). Furthermore, nearer the sea, fish would have been an important source of protein and polyunsaturated fats.

Although human studies are scarce on the epigenetic effects of such environments, camel's milk does appear to be protective against aspects of the metabolic syndrome (preventing T2DM) [83]. Studies in rural versus urbanised Saudi children show that the increase in asthma urban areas may well be due to adoption of a Western diet and the loss of a the traditional Arab diet, suggesting changes in the immune system [84]. Heat stress also has a powerful hormetic effect that can extend lifespan in several organisms [85], and recent research using mice suggests that heat stress may also reduce insulin resistance [86]. Dehydration is also an important stress, which stimulates anti-oxidant mechanisms in plants, as it induces mitochondrial oxidative stress, resulting in mechanisms to reduce ROS [87]. In mammalian cells, dehydration induces transfer of heat shock proteins to the mitochondrion [88]; this would also suggest an adaptive response to stress. Thus, the finding that resistance to one environmental stress, such as dehydration, can improve resistance to others, such as heat shock, and may correlate with improved longevity in fruit flies [89] – is highly suggestive that these factors may be important in the Gulf. Finally, the concept of 'xenohormesis' suggests that stress molecules produced by plants (such as polyphenols), can also be interpreted by animals and upregulate their resistance [90], may be very relevant.

It is therefore quite possible that the original harsh environment in the Gulf provided a powerful hormetic signal to the indigenous populations. With rapid modernisation, this signal has now been largely removed. This has most likely been due to rapid 'obesogenic urbanisation' across most socioeconomic groups, and the rapid adoption of modern labour saving devices (e.g. mechanised transport), as well as temperature control, plentiful supplies of water and a shift to a high calorie Western diet. Furthermore, the advent of the computer and quite possibly, a shift in leisure time activity away from physically active pastimes for the young has resulted in an increasingly sedentary lifestyle for youngsters in the Gulf. It has been previously estimated that nearly 60% of Saudi schoolchildren 70% of youth do not engage in sufficient physical activity [91]. Unfortunately, this tends to set the precedent for later life; up to 96% of Saudi adults have been classed as 'inactive' [92].

Finally, the influence of Ramadan may also need to be considered. Alternate day fasting has been shown to mimic the longevity inducing effects of calorie restriction in animals, and to demonstrate some beneficial alterations in biochemical markers in humans (although detailed human trials are limited at the present time). In essence, calories are restricted on alternate days, and may not necessarily result in a total reduced calorie input over a number of days, but do result in enough 'stress' to invoke improved metabolic flexibility. Interestingly, the effect seems to be more beneficial in men than women, with sex differences in lipid profiles (women tend to display an increase in HDL-c, whereas men tend to show reduced triglycerides). There is also evidence that liver triglycerides reduce, with some improvement in insulin sensitivity [93]. However, there is very little data studying Ramadan and the metabolic syndrome. In one trial, healthy men did show an improvement in insulin sensitivity during Ramadan, which correlated with a small decreased in calorie intake [94]. While in another involving T2DM subjects, there were clear sex differences. Although cholesterol intake increased in all (as did LDL-c), BMI tended to reduce in men, which was correlated with improved insulin sensitivity, but in women, BMI increased and was not correlated with any improvements [95]. It is thus quite likely that fasting (and dehydration), per se, is protective, but there are likely gender differences, both physiologically and culturally. Finally, the new field of chronobiology does suggest that shortage of sleep, or having large meals (especially of carbohydrate) late at night, can disrupt the circadian rhythm and could possibly accentuate the propensity to develop the metabolic syndrome. Critically, not only does it appear that adipose tissue may well have its own daily rhythm, but many important metabolic transcription factors, such as the PPARs, may also follow a circadian rhythm [96]. Thus, Ramadan could potentially be beneficial (as a hormetic stressor), but these benefits may be offset (especially when it falls during the summer with long daylight hours), by having large meals very late in the day (which may have become more westernised), and a reduction in sleep.

4.2. Rate of modernisation, epigenetic canalisation and Gulf hormesis

It is not just the loss of hormesis that may be important, but the speed at which it has happened in generational terms. In the West, the process of developing advanced civilisations that remove day-to-day 'stresses', which have made life easier, has been a gradual process over centuries and thus, 10–15 generations or more. Additionally, many of these Western cultures came from colder climates; this may confer some level of resistance to the metabolic syndrome – the so called 'cold genes' hypothesis [97]. Another cultural adaption has been the pursuit of physical activity to improve body image. An example of the rate of modernisation effect may be the observed higher rates of obesity and diabetes in the USA amongst the immigrant Hispanic population, compared with African American and Caucasians [7]; Hispanics migrated to the USA fairly recently, and have therefore been exposed to 'obesogenic urbanisation' within only a few generations. In contrast, African American have been exposed to it for 10 generations or more.

In the Gulf, not only is the climate warmer, but adoption of a western sedentary lifestyle has happened within the last 2–3 generations – and possibly even in the lifetime of some of those still alive today. Moreover, the highly generous nature of the indigenous peoples in relation to food giving has continued, especially of now readily available high calorie foods. Importantly, as the wealth has spread to most socioeconomic classes, high calorie food is now available to all. This has resulted in the development of a highly obesogenic environment in a very short period, where many grandparents may well have been exposed to times when food was much less plentiful.

In the Gulf, not only is the climate warmer, but adoption of a western sedentary lifestyle has happened within the last 2–3 generations – and possibly even in the lifetime of some of those still alive today. Moreover, the highly generous nature of the indigenous peoples in relation to food giving has continued, especially of now readily available high calorie foods. Importantly, as the wealth has spread to most socioeconomic classes, high calorie food is now available to all. This has resulted in the development of a highly obesogenic environment in a very short period, where many

grandparents may well have been exposed to times when food was much less plentiful.

This may have resulted in a thrifty phenotype being exposed to a continual supply of high calorie food, but because this phenotype is no longer hormetically challenged, it has become metabolically inflexible. This metabolic inflexibility is then propagated to the next generation as the mother develops the metabolic syndrome. One way to explain this is via the concept of "*genetic canalisation*" of the thrifty trait, which is probably a characteristic of all life. However, the expression of this trait is strongly modulated by the environment, both immediately in the individual (e.g. during famine), or by either exposure *in utero* to signals from the mother, or possibly from previous generational exposure to famine via epigenetic changes [3]. In effect, because resistance to famine is such an extremely strong survival trait, natural selection has resulted in it becoming resistant to mutational perturbation (thus, the environment will have a much stronger effect than individual polymorphisms on the expression of a particular phenotype). Without hormesis, the epigenotype canal may become narrower and the organism less metabolically flexible. In effect, hormesis broadens the canal, and thus, metabolic flexibility enabling the epigenotype to cope with a higher calorie intake – although it will be less energy efficient. In evolutionary terms, a narrow canal meant that the animal required fewer calories to survive, but was metabolically less flexible, however, it was unlikely that the canal would ever became too narrow, as it was always going to be exposed to some kind of stress (e.g. the need to move, or resist temperature extremes). Within these constraints, it was perfectly adapted. Hence, if exposed to calories, it would be in a position to store them.

However, the position in the Gulf is unusual. Fig. 6 depicts what the shape and breadth of the epigenetic canal may look like between an adapted population (e.g. the UK) and a population suddenly exposed to a non-hormetic environment (e.g. the Gulf) across three generations. In effect, the sudden loss of hormetic stimuli, coupled with increased food availability, both narrows the canal, and causes the expressed phenotype to move to the feast side. This phenotype, as it cannot deal with continual excessive calories, deposits ectopic fat (due to metabolic inflexibility) and becomes inflamed. This may be part of a mechanism to resist excessive weight gain, which induces lipolysis and activation of the stress response. It is possible that in the short term, this stress is itself hormetic, so widening the canal. However, if continually exposed to 'food stress' without other concurrent hormetic stimuli, the metabolic syndrome phenotype develops. This epigenotype can then be passed onto the next generation in a similar way to a thrifty epigenotype (e.g. by insulin resistance), however, as the next generation may also be exposed to an obesogenic environment, it may well be even less well adapted than the previous one. It is thus possible that with each successive Gulf generation, the epigenotype is becoming less and less flexible, with symptoms occurring at younger and younger ages.

5. Need for early detection and invocation of lifestyle change

In the West, it is only gradually becoming accepted that prevention is better than cure, as data, both clinically, and now, molecularly, indicates that a healthy lifestyle greatly slows the development of many diseases of aging. For instance, calorie restriction, and alternate day fasting are the only proven mechanisms for extending lifespan, while regular physical improves functional longevity. One of the core mechanisms revolves around reducing the activity of the insulin/insulin like growth factor axis, activating certain transcription factors and improving mitochondrial function [77,93,98–100]. The underlying principle of hormesis is even less well embraced. Indeed, in countries like the UK, the situation may be getting even worse as physical activity is systematically being reduced in schools and being replaced by a sedentary computer-based culture. In combination with the emergence of the credit society (and thus, access to money for lower socioeconomic groups, which has generated a perception of wealth and the ability to buy labour saving devices and high calorie food), this could be generating a metabolic syndrome time bomb. The is clearly supported by the fact that T2DM rates (in people aged between 10–79 years) in the UK have suddenly shot up from 2.6% in 1996, to 4.3% in 2005 [101]. This probably represents the development of an obesogenic environment in a society that has already adapted to wealth over many generations.

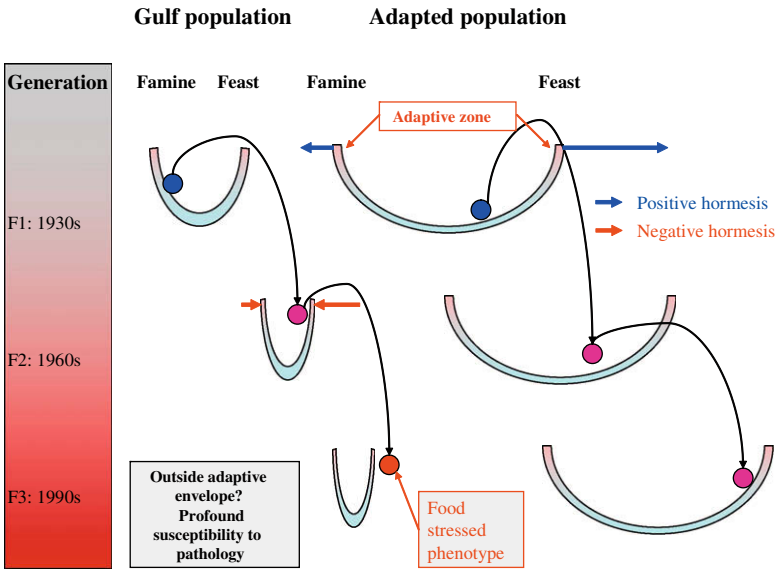


Fig. 6. Epigenetic canalisation and transfer of 'stress' signal (e.g. insulin resistance) through Gulf generations due to lack of hormesis. The ball represents the current phenotype and the canal, the epigenotype. Energy requiring hormetic factors such as exercise, temperature extremes, drought & stress polyphenols widen the canal to the right, whereas energy reducing factors, such as famine/fasting, widen it to the left. Metabolic flexibility is improved in both directions, but famine/fasting reduces energy expenditure, while energy requiring factors increase it. Without any hormetic factors, the canal becomes so narrow that in the presence of excess food, the phenotype falls outside and becomes permanently stressed: this is then passed on to the next generation, so perpetuating the problem.

The answer, in part, is to invoke a societal change in lifestyle behaviour based on early detection of the condition and to educate on its implications with regards to absolute and healthy life expectancy. The general public is unaware that T2DM is the culmination of many years of a combination of poor lifestyle coupled to a general human predisposition to the condition, which is already shortening their quality of life and their life expectancy. One of the best ways to do this may be to study fat distribution and the presence of ectopic fat.

5.1. Early detection

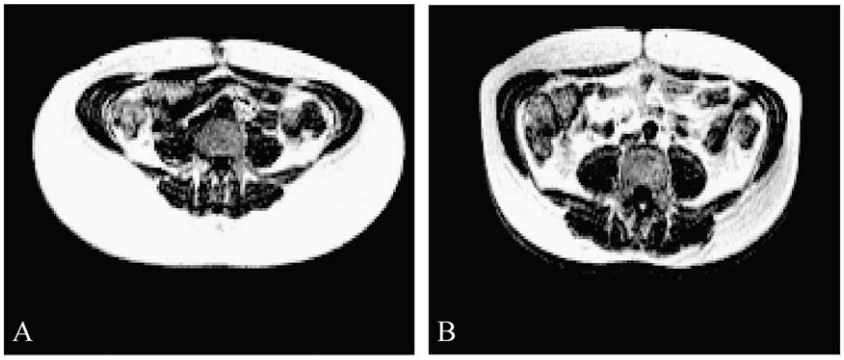
Clearly, individuals who are overweight and already displaying signs of the metabolic syndrome, especially if they are very unfit and older, are easily identifiable: they are both fat on the outside, and the inside (FOFI). However, the population is the Gulf is still very young. As current metabolic syndrome definitions will not pick up early indications, there is a need for new methods of early detection. It needs to be remembered that these definitions are also based on western populations and quite possibly, on population averages, and not necessarily what is actually healthy. In the USA, the majority of T2DM patients do not reach their treatment goals for HbA1c, which is less than 7%, however, in reality, the risk of T2DM increases from about 4.6%, which is about the same point that the risk of microvascular disease also rises [102,103]. Thus, many people will be displaying above normal HbA1c long before being diagnosed as diabetic. In an important time period may be during childhood and adolescence, as this is when maximum growth occurs: this may mask the effect (as calories get used towards growing), but a corollary to this is that insulin resistance may also stunt growth. Insulin resistance, as a thrifty mechanism, encourages deposition of fat in adipose tissue rather using it to build lean muscle tissue – 'catch up growth' [104]. Hence, their may be an adolescent tipping point.

One of the strongest markers for metabolic inflexibility is the presence of ectopic fat, such is in the visceral region, the liver, muscle or even around the aorta [56,105,106]; thus assessing fat distribution is becoming paramount. One very powerful method to achieve this is a combination of magnetic resonance imaging and spectroscopy. We have studied more than 1000 volunteers and shown that fat distribution correlates very strongly with other risk markers, such a lack of fitness, dyslipidaemia, blood pressure and markers of insulin resistance, as well as the presence of fat in the liver [107]. We have also shown that these changes can be measured in pre-term infants [108], and that exercise can dramatically reduce visceral fat volume [109]. It is becoming increasingly apparent that it is possible to be fat outside and thin inside (FOTI), and thin outside and fat inside (TOFI) – with the latter being a much riskier phenotype. Fig. 7 shows a typical MRI scan of two people with near identical BMI, but vastly differing risk profiles.

5.2. The future

A number of studies are suggesting that, if left untouched, some populations in the Gulf will have dramatically shortened life expectancies, enduring significant morbidity for up to a third of their lives. This may well greatly reduce the capacity of a population to compete in a modern world. Darwin had, over a 130 years ago, unwittingly via the concept of natural selection, laid the seeds for an idea that some populations could modify their environment so successfully that their new environment would actually become detrimental. This has been called *evolutionary suicide*, or *Darwinian extinction* [110]. The Gulf Metabolic Syndrome could be an example of such a process in action. In particular, conditions such as PCOS, may well be the harbinger of this – if rates are shown to be increasing in the Gulf, especially in young women; loss of fertility in this age group could have a serious impact on society. Furthermore, in one study in Saudi Arabia, overall 86.1% of non-insulin dependent diabetic patients had evidence of erectile dysfunction; worryingly, the rate was 25% in men aged under 50 years [111]. With a diabetic rate approaching 1 in 3, it is possible that 1 in 4 men may already be experiencing problems.

However, this does not need to be the case. The metabolic syndrome is largely, if not completely, preventable and/or reversible. Physical activity is one of the most potent preventative mechanisms known, and is explainable at the molecular level. Moreover, there are many other hormetic factors that can help to induce biological fitness to survive in a modern world, ranging for plant polyphenols, to temperature stress, to fasting. The last of these, epitomised by calorie restriction, is the only really reliable mechanism to greatly extend lifespan and the molecular signature is observable in humans undergoing calorie restriction [112]. Unfortunately, as the propensity to develop the metabolic syndrome without hormesis is emerging as an inherent property for many animals, including humans, then the Gulf has no option but to radically change its environment to optimise the fitness of its citizens. The first step will be to make people aware of what is actually happening to them: this will require a very bold programme of early screening, development of new definitions and guidelines, and instigation of preventative lifestyle measures – something the developed nations have not been able to do as yet. The Gulf may have the biggest problem, but it may also, because of its culture, be the first to be able to develop a societal-wide paradigm to control the inexorable rise of the metabolic syndrome.



Subject A: BMI 28.5 kg/m², 1.3 litres visceral adipose tissue
Subject B: BMI 28.8 kg/m², 5.5 litres visceral adipose tissue

Fig. 7. A FOTI subject versus a TOFI subject.

6. Conclusion

Because of oil wealth, the Gulf has experienced an unprecedentedly rapid evolution of 'obesogenic urbanisation' across all socioeconomic classes. This has resulted in the loss of hormetic factors within epigenetic memory of harder times, which has resulted in the generation, and then perpetuation of metabolically inflexible subsequent generations totally unable to deal with a Western high calorie diet. This is resulting in the 'metabolic syndrome' phenotype being expressed at younger and younger ages, which is very likely to result in a substantial reduction in both healthy and absolute life expectancy. In effect, because thriftiness has become a genetically canalised trait common to all animals, benign insulin resistance has become malignant, which is associated with obesity and diabetes. This could lead to Darwinian extinction of some populations due to accelerated ageing and early loss of fertility. However, as this probably only goes back in two to three generations, there is a very good chance that this could be rapidly reversed by lifestyle modification. Research therefore needs to focus on the young and early detection of this condition and reversal by reintroduction of a more 'hormetic' lifestyle.

References

[1] Diet, nutrition and the prevention of chronic diseases. World Health Organ Tech Rep Ser; 2003. 916, i-149, backcover.
[2] Amuna P, Zotor FB. Epidemiological and nutrition transition in developing countries: impact on human health and development. Proc Nutr Soc 2008;67:82–90.
[3] Stoger R. The thrifty epigenotype: an acquired and heritable predisposition for obesity and diabetes? Bioessays 2008;30:156–66.
[4] Storlien L, Oakes ND, Kelley DE. Metabolic flexibility. Proc Nutr Soc 2004;63:363–8.
[5] Rattan SI. Aging intervention, prevention, and therapy through hormesis. J Gerontol A Biol Sci Med Sci 2004;59:705–9.
[6] Nunn AV, Bell JD, Guy GW. Lifestyle-induced metabolic inflexibility and accelerated ageing syndrome: insulin resistance, friend or foe? Nutr Metab (Lond) 2009;6:16.
[7] Narayan KM, Boyle JP, Thompson TJ, Gregg EW, Williamson DF. Effect of BMI on lifetime risk for diabetes in the U.S.. Diabetes Care 2007;30:1562–6.
[8] Keaney Jr JF, Larson MG, Vasan RS, Wilson PW, Lipinska I, Corey D, et al. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham study. Arterioscler Thromb Vas Biol 2003;23:434–9.
[9] Olusi SO. Obesity is an independent risk factor for plasma lipid peroxidation and depletion of erythrocyte cytoprotectic enzymes in humans. Int J Obes Relat Metab Disord 2002;26:1159–64.
[10] Esposito K, Giugliano F, Ciotola M, De SM, D'Armiento M, Giugliano D. Obesity and sexual dysfunction, male and female. Int J Impot Res 2008;20:358–65.
[11] Dunbar JA, Reddy P, vis-Lameloise N, Philpot B, Laatikainen T, Kilkkinen A, et al. Depression: an important comorbidity with metabolic syndrome in a general population. Diabetes Care 2008;31:2368–73.
[12] Roriz-Filho S, Sa-Roriz TM, Rosset I, Camozzato AL, Santos AC, Chaves ML, Moriguti JC, Roriz-Cruz M. (Pre)diabetes, brain aging, and cognition. Biochim Biophys Acta; 16-12-2008.
[13] von MD, Safii S, Jassal SK, Svartberg J, Barrett-Connor E. Associations between the metabolic syndrome and bone health in older men and women: the Rancho Bernardo study. Osteoporos Int 2007;18:1337–44.
[14] Wahba IM, Mak RH. Obesity and obesity-initiated metabolic syndrome: mechanistic links to chronic kidney disease. Clin J Am Soc Nephrol 2007;2:550–62.
[15] Zhou JR, Blackburn GL, Walker WA. Symposium introduction: metabolic syndrome and the onset of cancer. Am J Clin Nutr 2007;86:s817–9.
[16] Galluzzo A, Amato MC, Giordano C. Insulin resistance and polycystic ovary syndrome. Nutr Metab Cardiovasc Dis 2008;18:511–8.
[17] Armitage JA, Taylor PD, Poston L. Experimental models of developmental programming: consequences of exposure to an energy rich diet during development. J Physiol 2005;565:3–8.
[18] Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The metabolic syndrome: a global public health problem and a new definition. J Atheroscler Thromb 2005;12:295–300.
[19] Moebus S, Hanisch JU, Aidelsburger P, Bramlage P, Wasem J, Jockel KH. Impact of 4 different definitions used for the assessment of the prevalence of the metabolic syndrome in primary healthcare: the German metabolic and cardiovascular risk project (GEMCAS). Cardiovasc Diabetol 2007;6:22.
[20] Wu CH, Heshka S, Wang J, Pierson Jr RN, Heymsfield SB, Laferrere B, et al. Truncal fat in relation to total body fat. Influences of age, sex, ethnicity and fatness. Int J Obes (Lond) 2007;31:1384–91.
[21] Gao. Does diagnosis of the metabolic syndrome detect further men at high risk of cardiovascular death beyond those identified by a conventional cardiovascular risk score? The DECODE Study. Eur J Cardiovasc Prev Rehabil 2007;14:192–9.
[22] Monteiro CA, Conde WL, Popkin BM. Income-specific trends in obesity in Brazil: 1975–2003. Am J Public Health 2007;97:1808–12.
[23] Al-Baghli NA, Al-Ghamdi AJ, Al-Turki KA, El-Zubaier AG, Al-Ameer MM, Al-Baghli FA. Overweight and obesity in the eastern province of Saudi Arabia. Saudi Med J 2008;29:1319–25.
[24] Al-Nozha MM, Al-Mazrou YY, Al-Maatouq MA, Arafah MR, Khalil MZ, Khan NB, et al. Obesity in Saudi Arabia. Saudi Med J 2005;26:824–9.
[25] Al-Othaimeen AI, Al-Nozha M, Osman AK. Obesity: an emerging problem in Saudi Arabia. Analysis of data from the national nutrition survey. East Mediterr Health J 2007;13:441–8.
[26] Al-Hazzaa HM. Prevalence and trends in obesity among school boys in Central Saudi Arabia between 1988 and 2005. Saudi Med J 2007;28:1569–74.
[27] Al-Isa AN. Are Kuwaitis getting fatter? Nutr Health 2003;17:185–97.
[28] Al-Nuaim RA. Population-based epidemiological study of the prevalence of overweight and obesity in Saudi Arabia, regional variation. Ann Saudi Med 1997;17:195–9.
[29] Gregg EW, Cheng YJ, Cadwell BL, Imperatore G, Williams DE, Flegal KM, et al. Secular trends in cardiovascular disease risk factors according to body mass index in US adults. JAMA 2005;293:1868–74.
[30] Musaiger AO, Al-Mannai MA. Weight, height, body mass index and prevalence of obesity among the adult population in Bahrain. Ann Hum Biol 2001;28:346–50.
[31] Yach D, Stuckler D, Brownell KD. Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. Nat Med 2006;12:62–6.
[32] Al Turki YA. Overweight and obesity among attendees of primary care clinics in a university hospital. Ann Saudi Med 2007;27:459–60.
[33] Al-Nozha MM, Al-Maatouq MA, Al-Mazrou YY, Al-Harthi SS, Arafah MR, Khalil MZ, et al. Diabetes mellitus in Saudi Arabia. Saudi Med J 2004;25:1603–10.
[34] Al-Hazzaa HM, Al-Rasheedi AA. Adiposity and physical activity levels among preschool children in Jeddah, Saudi Arabia. Saudi Med J 2007;28:766–73.
[35] Al-Isa AN. Body mass index, overweight and obesity among Kuwaiti intermediate school adolescents aged 10–14 years. Eur J Clin Nutr 2004;58:1273–7.
[36] Sorkhou I, Al-Qallaf K, Al-Shamali N, Hajia A, Al-Qallaf B. Childhood obesity in Kuwait – prevalence and trends. Fam Med 2003;35:463–4.
[37] Al-Turki YA. Overweight and obesity among attendees of primary care clinics in a university hospital. Ann Saudi Med 2007;27:59–60.
[38] Al-Kandari YY. Prevalence of obesity in Kuwait and its relation to sociocultural variables. Obes Rev 2006;7:147–54.
[39] Alsmadi O, Al-Rubeaan K, Wakil SM, Imtiaz F, Mohamed G, Al-Saud H, et al. Genetic study of Saudi diabetes (GSSD): significant association of the KCNJ11 E23K polymorphism with type 2 diabetes. Diabetes Metab Res Rev 2008;24:137–40.
[40] Al-Nozha M, Al-Khadra A, Arafah MR, Al-Maatouq MA, Khalil MZ, Khan NB, et al. Metabolic syndrome in Saudi Arabia. Saudi Med J 2005;26:1918–25.
[41] Al-Shaibani H, El-Batish M, Sorkhou I, Al-Shamali N, Al-Namash H, Habiba S, et al. Prevalence of insulin resistance syndrome in a primary health care center in Kuwait. Fam Med 2004;36:540.
[42] Cameron AJ, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. Endocrinol Metab Clin North Am 2004;33:351–75 [Table].
[43] Lorenzo C, Williams K, Hunt KJ, Haffner SM. Trend in the prevalence of the metabolic syndrome and its impact on cardiovascular disease incidence: the San Antonio heart study. Diabetes Care 2006;29:625–30.
[44] Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham risk score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Int Med 2005;165:2644–50.
[45] Al Bustan M, Batistella R. The Kuwaiti national health service: financial restraints and cost sharing imperatives. Int J Health Plan Meas 1998;3:259–72.
[46] Al-Ajlan A. Diabetic scenario in Arabs. Saudi Med J 2007;28:473–5.
[47] el-Hazmi MA, Warsy AS, al-Swailem AR, al-Swailem AM, Sulaimani R, Al-Meshari AA. Diabetes mellitus and impaired glucose tolerance in Saudi Arabia. Ann Saudi Med 1996;16:381–5.
[48] Abdella N, Al AM, Al NA, Al AA, Moussa M. Non-insulin-dependent diabetes in Kuwait: prevalence rates and associated risk factors. Diabetes Res Clin Pract 1998;42:187–96.
[49] Saadi H, Carruthers SG, Nagelkerke N, Al-Maskari F, Afandi B, Reed R, et al. Prevalence of diabetes mellitus and its complications in a population-based sample in Al Ain, United Arab Emirates. Diabetes Res Clin Pract 2007;78:369–77.

[50] Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Int Med 2001;161:1581–6.
[51] Pitsavos C, Panagiotakos D, Weinem M, Stefanadis C. Diet, exercise and the metabolic syndrome. Rev Diabet Stud 2006;3:118–26.
[52] Rector RS, Warner SO, Liu Y, Hinton PS, Sun GY, Cox RH, et al. Exercise and diet induced weight loss improves measures of oxidative stress and insulin sensitivity in adults with characteristics of the metabolic syndrome. Am J Physiol Endocrinol Metab 2007;293:E500–6.
[53] Heilbronn L, Smith SR, Ravussin E. Failure of fat cell proliferation, mitochondrial function and fat oxidation results in ectopic fat storage, insulin resistance and type II diabetes mellitus. Int J Obes Relat Metab Disord 2004;28(Suppl. 4):S12–21.
[54] Szendroedi J, Roden M. Ectopic lipids and organ function. Curr Opin Lipidol 2009;20:50–6.
[55] Chanseaume E, Tardy AL, Salles J, Giraudet C, Rousset P, Tissandier A, et al. Chronological approach of diet-induced alterations in muscle mitochondrial functions in rats. Obesity (Silver Spring) 2007;15:50–9.
[56] Schlett CL, Massaro JM, Lehman SJ, Bamberg F, O'Donnell CJ, Fox CS, et al. Novel measurements of periaortic adipose tissue in comparison to anthropometric measures of obesity, and abdominal adipose tissue. Int J Obes (Lond) 2009;33:226–32.
[57] Nunn AV, Bell J, Barter P. The integration of lipid-sensing and anti-inflammatory effects: how the PPARs play a role in metabolic balance. Nucl Recept 2007;5:1.
[58] Freedland ES. Role of a critical visceral adipose tissue threshold (CVATT) in metabolic syndrome: implications for controlling dietary carbohydrates: a review. Nutr Metab (Lond) 2004;1:12.
[59] Nunn AV, Guy GW, Bell JD. Endocannabinoids, FOXO and the metabolic syndrome: redox, function and tipping point – the view from two systems. Immunobiology 2009.
[60] Laplante M, Festuccia WT, Soucy G, Gelinas Y, Lalonde J, Berger JP, et al. Mechanisms of the depot specificity of peroxisome proliferator-activated receptor gamma action on adipose tissue metabolism. Diabetes 2006;55:2771–8.
[61] Deveaud C, Beauvoit B, Salin B, Schaeffer J, Rigoulet M. Regional differences in oxidative capacity of rat white adipose tissue are linked to the mitochondrial content of mature adipocytes. Mol Cell Biochem 2004;267:157–66.
[62] Henry BA, Dunshea FR, Gould M, Clarke IJ. Profiling postprandial thermogenesis in muscle and fat of sheep and the central effect of leptin administration. Endocrinology 2008;149:2019–26.
[63] Hudson NJ, Lehnert SA, Harper GS. Obese humans as economically designed feed converters: symmorphosis and low oxidative capacity skeletal muscle. Med Hypotheses 2007.
[64] Incerpi S, Fiore AM, De VP, Pedersen JZ. Involvement of plasma membrane redox systems in hormone action. J Pharm Pharmacol 2007;59:1711–20.
[65] Menon SG, Goswami PC. A redox cycle within the cell cycle: ring in the old with the new. Oncogene 2007;26:1101–9.
[66] Erusalimsky JD, Moncada S. Nitric oxide and mitochondrial signaling. from physiology to pathophysiology. Arterioscler Thromb Vas Biol 2007;27:2524–31.
[67] Parsons PA. Antagonistic pleiotropy and the stress theory of aging. Biogerontology 2007;8:613–7.
[68] Tapia PC. Sublethal mitochondrial stress with an attendant stoichiometric augmentation of reactive oxygen species may precipitate many of the beneficial alterations in cellular physiology produced by caloric restriction, intermittent fasting, exercise and dietary phytonutrients: "Mitohormesis" for health and vitality. Med Hypotheses 2006;66:832–43.
[69] Muzumdar R, Allison DB, Huffman DM, Ma X, Atzmon G, Einstein FH, et al. Visceral adipose tissue modulates mammalian longevity. Aging Cell 2008;7:438–40.
[70] Kinsella KG. Changes in life expectancy 1900–1990. Am J Clin Nutr 1992;55:1196S–202S.
[71] Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med 2005;352:1138–45.
[72] Robert L, Robert AM, Fulop T. Rapid increase in human life expectancy: will it soon be limited by the aging of elastin? Biogerontology 2008;9:119–33.
[73] Mathers CD, Iburg KM, Salomon JA, Tandon A, Chatterji S, Ustun B, et al. Global patterns of healthy life expectancy in the year 2002. BMC Public Health 2004;4:66.
[74] Robine JM, Ritchie K. Healthy life expectancy: evaluation of global indicator of change in population health. BMJ 1991;302:457–60.
[75] Romero DE, Leite IC, Szwarcwald CL. Healthy life expectancy in Brazil: applying the Sullivan method. Cad Saude Publica 2005;21(Suppl.):7–18.
[76] Dwyer J. Starting down the right path: nutrition connections with chronic diseases of later life. Am J Clin Nutr 2006;83:415S–20S.
[77] Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ 2006;174:801–9.
[78] Li TY, Rana JS, Manson JE, Willett WC, Stampfer MJ, Colditz GA, et al. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. Circulation 2006;113:499–506.
[79] Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–38.
[80] Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. JAMA 2003;289:187–93.
[81] Haslam DW, James WP. Obesity. Lancet 2005;366:1197–209.
[82] Roglic G, Unwin N, Bennett PH, Mathers C, Tuomilehto J, Nag S, et al. The burden of mortality attributable to diabetes: realistic estimates for the year 2000. Diabetes Care 2005;28:2130–5.
[83] Agrawal RP, Budania S, Sharma P, Gupta R, Kochar DK, Panwar RB, et al. Zero prevalence of diabetes in camel milk consuming Raica community of north–west Rajasthan, India. Diabetes Res Clin Pract 2007;76:290–6.
[84] Hijazi N, Abalkhail B, Seaton A. Diet and childhood asthma in a society in transition: a study in urban and rural Saudi Arabia. Thorax 2000;55:775–9.
[85] Rattan SI, Gonzalez-Dosal R, Nielsen ER, Kraft DC, Weibel J, Kahns S. Slowing down aging from within: mechanistic aspects of anti-aging hormetic effects of mild heat stress on human cells. Acta Biochim Pol 2004;51:481–92.
[86] Kokura S, Adachi S, Manabe E, Mizushima K, Hattori T, Okuda T, et al. Whole body hyperthermia improves obesity-induced insulin resistance in diabetic mice. Int J Hyperthermia 2007;23:259–65.
[87] Pastore D, Trono D, Laus MN, Di FN, Flagella Z. Possible plant mitochondria involvement in cell adaptation to drought stress. A case study: durum wheat mitochondria. J Exp Bot 2007;58:195–210.
[88] Itoh H, Komatsuda A, Ohtani H, Wakui H, Imai H, Sawada K, et al. Mammalian HSP60 is quickly sorted into the mitochondria under conditions of dehydration. Eur J Biochem 2002;269:5931–8.
[89] Bubliy OA, Loeschcke V. Correlated responses to selection for stress resistance and longevity in a laboratory population of Drosophila melanogaster. J Evol Biol 2005;18:789–803.
[90] Lamming DW, Wood JG, Sinclair DA. Small molecules that regulate lifespan: evidence for xenohormesis. Mol Microbiol 2004;53:1003–9.
[91] Al-Hazzaa HM. Pedometer-determined physical activity among obese and non-obese 8- to 12-year-old Saudi schoolboys. J Physiol Anthropol 2007;26:459–65.
[92] Al-Nozha MM, Al-Hazzaa HM, Arafah MR, Al-Khadra A, Al-Mazrou YY, Al-Maatouq MA, et al. Prevalence of physical activity and inactivity among Saudis aged 30–70 years. A population-based cross-sectional study. Saudi Med J 2007;28:559–68.
[93] Varady KA, Hellerstein MK. Alternate-day fasting and chronic disease prevention: a review of human and animal trials. Am J Clin Nutr 2007;86:7–13.
[94] Shariatpanahi ZV, Shariatpanahi MV, Shahbazi S, Hossaini A, Abadi A. Effect of Ramadan fasting on some indices of insulin resistance and components of the metabolic syndrome in healthy male adults. Br J Nutr 2008;100:147–51.
[95] Yarahmadi S, Larijani B, Bastanhagh MH, Pajouhi M, Baradar JR, Zahedi F, et al. Metabolic and clinical effects of Ramadan fasting in patients with type II diabetes. J Coll Physicians Surg Pak 2003;13:329–32.
[96] Garaulet M, Madrid JA. Chronobiology, genetics and metabolic syndrome. Curr Opin Lipidol 2009;20:127–34.
[97] Fridlyand LE, Philipson LH. Cold climate genes and the prevalence of type 2 diabetes mellitus. Med Hypotheses 2006;67:1034–41.
[98] Handschin C, Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. Nature 2008;454:463–9.
[99] Jonker JT, De Laet C, Franco OH, Peeters A, Mackenbach J, Nusselder WJ. Physical activity and life expectancy with and without diabetes: life table analysis of the Framingham heart study. Diabetes Care 2006;29:38–43.
[100] Salih DA, Brunet A. FoxO transcription factors in the maintenance of cellular homeostasis during aging. Curr Opin Cell Biol 2008;20:126–36.
[101] González EL, Johansson S, Wallander MA, Rodríguez LA. Trends in the prevalence and incidence of diabetes in the UK: 1996–2005. J Epidemiol Commun Health 2009;63:332–6.
[102] Edelman D, Olsen MK, Dudley TK, Harris AC, Oddone EZ. Utility of hemoglobin A1c in predicting diabetes risk. J Gen Int Med 2004;19:1175–80.
[103] Stolar MW, Hoogwerf BJ, Gorshow SM, Boyle PJ, Wales DO. Managing type 2 diabetes: going beyond glycemic control. J Manag Care Pharm 2008;14:s2–19.
[104] Dulloo AG, Jacquet J, Seydoux J, Montani JP. The thrifty 'catch-up fat' phenotype: its impact on insulin sensitivity during growth trajectories to obesity and metabolic syndrome. Int J Obes (Lond) 2006;30(Suppl. 4):S23–35.

[105] van der PD, Milner KL, Hui J, Hodge A, Trenell MI, Kench JG, et al. Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. Hepatology 2008;48:449–57.
[106] Yim JE, Heshka S, Albu J, Heymsfield S, Kuznia P, Harris T, et al. Intermuscular adipose tissue rivals visceral adipose tissue in independent associations with cardiovascular risk. Int J Obes (Lond) 2007;31:1400–5.
[107] Thomas EL, Hamilton G, Patel N, O'Dwyer R, Dore CJ, Goldin RD, et al. Hepatic triglyceride content and its relation to body adiposity: a magnetic resonance imaging and proton magnetic resonance spectroscopy study. Gut 2005;54:122–7.
[108] Thomas EL, Uthaya S, Vasu V, McCarthy JP, McEwan P, Hamilton G, et al. Neonatal intrahepatocellular lipid. Arch Dis Child Fetal Neonatal Ed 2008;93:F382–3.
[109] Thomas EL, Brynes AE, McCarthy J, Goldstone AP, Hajnal JV, Saeed N, et al. Preferential loss of visceral fat following aerobic exercise, measured by magnetic resonance imaging. Lipids 2000;35:769–76.
[110] Webb C. A complete classification of Darwinian extinction in ecological interactions. Am Nat 2003;161:181–205.
[111] El-Sakka AI, Tayeb KA. Erectile dysfunction risk factors in noninsulin dependent diabetic Saudi patients. J Urol 2003;169:1043–7.
[112] Civitarese AE, Carling S, Heilbronn LK, Hulver MH, Ukropcova B, Deutsch WA, et al. Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. PLoS Med 2007;4:e76.

Geoffrey W. Guy [a]
Alistair V.W. Nunn [b,c,*]
Louise E. Thomas [c]
Jimmy D. Bell [c]
[a] *Porton Down, Salisbury, Wiltshire, UK*
[b] *GW Pharmaceuticals, Porton Down, Dorset, UK*
[c] *Metabolic and Molecular Imaging Group, MRC Clinical Sciences Centre, Hammersmith Hospital, Imperial College London, Du Cane Road, London W12 OHS, UK*
* Corresponding author. Address: *Metabolic and Molecular Imaging Group, MRC Clinical Sciences Centre, Hammersmith Hospital, Imperial College London, Du Cane Road, London W12 OHS, UK.*
E-mail addresses: gwg@gwpharm.com (G.W. Guy), alistair.nunn@btconnect.com (A.V.W. Nunn), louise.thomas@csc.mrc.ac.uk (L.E. Thomas), jimmy.bell@csc.mrc.co.uk (J.D. Bell)