Psychological underpinnings of metabolic syndrome

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Metabolic syndrome (MS) is more common among socio-economically disadvantaged individuals and is associated with certain risky lifestyle practices. MS also appears to be triggered by adverse social circumstances and chronic stress. The present paper reviews accumulating evidence to imply that individuals who have certain personality and behaviour traits are particularly predisposed to develop MS, and brings together theories that relate to possible psychological mechanisms underlying MS. It considers how such factors might interact causally to encourage the development of MS. As part of the EU-funded LIPGENE Integrated Project, multi-level modelling will be undertaken to explore potential pathways to MS, taking into consideration the interplay between a range of psycho-social, demographic, cultural and lifestyle factors thought to contribute to the development of MS. Data will be gathered for this purpose from a representative sample of >50-year-olds living in Britain (*n* 1000) and Portugal (*n* 500). It is anticipated that this information will assist in the development and targetting of future intervention to prevent and treat MS in the normal population.

Metabolic syndrome: Psychological: Social: Demographic: Cultural

Obesity is a growing problem in Europe, currently affecting between 10 and 20% of the population (Buttriss, 2003). Understanding the various factors that have contributed to this trend and understanding why obesity is so difficult to treat has become an increasingly important health issue. The metabolic syndrome (MS; also known as syndrome X, insulin resistance syndrome, dysmetabolic syndrome, deadly quartet and plurimetabolic syndrome) is a cluster of factors associated with increased risk of developing CHD and/or type 2 diabetes. MS comprises insulin resistance (fasting blood sugar >10 mg/l), dyslipidaemia (triacylglycerol ≥15 mg/l, HDL <4 mg/l for men and 5 mg/l for women, LDL >15 mg/l), essential hypertension (blood pressure of ≥130 mmHg for systolic and ≥85 mmHg for diastolic) and visceral obesity (waist circumference of >1020 mm for men and >890 mm for women; Meigs *et al*. 1997; Roth *et al*. 2002).

MS, which is an antecedent of heart disease and type 2 diabetes, appears to be partly hereditary, may have its roots in early childhood, tends to develop with age and is exacerbated by poor diet and sedentary lifestyle (Raikkonen *et al*. 2003). There is substantial evidence to suggest that the condition is lifestyle related (McCaffery *et al*. 2003) and, if noticed early enough, can be reversed through dietary change and increased physical activity (Roth *et al*. 2002). Both large cross-sectional studies (Paffenbarger *et al*. 1978; Rennie *et al*. 2003) and longitudinal studies (Laaksonen *et al*. 2002, 2003) have shown that MS is less common among those individuals who take regular vigorous and moderate physical exercise and who eat a healthy diet (Lidfeldt *et al*. 2003). Lifestyle is only one among many factors that may contribute to risk for MS and consequently CHD and type 2 diabetes. MS may also be characterised by certain psychological traits and behaviours, emotional states and social circumstances. If the association between MS and these factors is verified, other new possibilities will emerge for successful intervention to prevent and treat MS before CHD and type 2 diabetes actually develop.

There is substantial evidence for a psycho-social component in the aetiology of CHD and emerging evidence that psychological factors may also contribute to the development of type 2 diabetes (Niaura, 2002). Stress (both acute and chronic), certain psychopathologies and adverse social conditions appear to be associated with increased risk of CVD (Kiecolt-Glaser *et al*. 2002). There is also growing evidence in recent literature that implies that MS may be triggered and/or exacerbated by adverse

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social factors (Horsten *et al*. 1999) and certain psycho-logical pathologies (Kinder *et al*. 2004), traits and behaviours (Raikkonen *et al*. 2003). Based on this interrelationship, intervention to reduce psychological distress could avoid the development of MS and poten-tially prevent or retard subsequent development of CHD and type 2 diabetes in susceptible individuals and groups. It is, therefore, becoming increasingly important to estab-lish the extent to which psychological factors contribute to MS. The purpose of the present mini-review is therefore to explore existing recent literature to assist in generating hypotheses for further study to determine and explore interrelationships between relevant psychological and social drivers of obesity and MS and related disease outcomes.

Could metabolic syndrome be triggered and/or exacerbated by psycho-social factors?

The role of negative emotions in the development of CHD is well established. The term 'type A' was originally coined by Friedman & Rosenman (1959) to refer to what they postulated to be a 'coronary-prone' behaviour pattern. The type A pattern is characterised by competitiveness, time urgency, impatience and hostility. Individuals with a type A pattern have been described as aggressive, dominant, quick-witted, self-confident, autonomous and extraverted. The trait is measured using the Minnesota Multiphasic Personality Inventory-derived Scale (Cook & Medley, 1954). Hostility, which is part of what comprises the type A pattern, has been defined as a mixture of anger and disgust often accompanied by indignation, contempt and resentment (Plutchik, 1980). Hostility appears to be stable over a period of time (Woodall & Matthews, 1993), suggesting that it could in itself be considered a trait. Anger, on the other hand, is a state of arousal that comprises behavioural, subjective, visceral and somatic components, and has been defined as the 'urge to attack' and as 'the opposite of fear' (Danesh, 1977). Anger is commonly assessed using the Trait Anger Questionnaire and the Anger Expression Scale (Spielberger, 1983). Both hostility and anger are commonly observed among those with high blood pressure and are associated with increased risk of heart disease (Haynes *et al*. 1980; Niaura, 2002).

Clinical features of MS are commonly observed among those individuals with a type A coronary-prone behaviour pattern (Ravaja *et al*. 1996). MS and CHD may, however, have different psychological precursors. Several studies have considered hostility and anger in relation to various anthropometric and biochemical markers for MS. Obesity and insulin resistance appear to be consistently related to hostility through childhood (Raikkonen *et al*. 2003). Associations between hostility and clinical features of MS, however, become less tenuous in adulthood. Earlier research by the same group (Raikkonen *et al*. 1996) has considered anger, hostility and type A behaviour as well as tiredness in Finnish middle-aged males (*n* 90) in relation to anthropometric, demographic and lifestyle practices, and has found no associations between type A behaviour or hostility and any of the metabolic factors associated with MS. Waist:hip ratio was, however, found to be related to high exhaustion and anger expression. A more recent study, which includes both male and female middle-aged civil servants and is part of the Whitehall II study (Feldman & Steptoe, 2003), has also found no relationship between markers of impaired glucose metabolism and hostility. Only one study (Niaura *et al*. 2000) appears to have found evidence of hostility in males with MS. Together the evidence suggests that there may be gender differences in the way psychological and metabolic factors interact in MS. A longitudinal cohort study of middle-aged women has indicated increased risk of MS among those who experience high levels of anger (Raikkonen *et al*. 2002). Further evidence that negative emotions could be particularly detrimental to women's health comes from a study that used computed tomography scanning (Raikko-nen *et al*. 1999*a*,*b*). This study indicates that hostility and anger contribute to visceral adipose tissue to a similar extent to smoking, alcohol or lack of physical activity in post-menopausal women. Current knowledge therefore implies that hostility may be particularly detrimental to women's health.

Chronic stress (Bjorntorp & Rosmond, 1999; Waldstein *et al*. 1999; Bjorntorp, 2000; Brunner *et al*. 2002; Vitaliano *et al*. 2002; Steptoe & Marmot, 2003) and stressful life events (Ravaja *et al*. 1996) have been linked to the development of abdominal obesity. Abdominal obesity is also commonly observed among sufferers of clinical depression (Weber-Hamann *et al*. 2002; McElroy *et al*. 2004), as well as in depressed (McCaffery *et al*. 2003; Kinder *et al*. 2004) and anxious (Landen *et al*. 2004) non-clinical populations. Depression may be more deleterious to women's health than to men's health. A large population study (*n* 3186; Kinder *et al*. 2004) has found a higher incidence of MS among young women (but not men) with a history of depression when other factors associated with MS are controlled. Features of MS also appear more common among women experiencing social anxiety (Landen *et al*. 2004). Again, this finding suggests gender differences in how MS develops and underlines the importance of including both genders in research exploring obesity in chronic disease pathways. Existing research, therefore, implies the possibility of different gender-specific causal pathways to MS.

Socio-economic deprivation has been shown to increase with age and to be associated with greater ill health in later years (Frost *et al*. 2001). Clinical features of MS are more commonly observed among more socio-economically disadvantaged individuals (Bjorntorp, 2000), in individuals who have spent less time in education (Wamala *et al*. 1999; Kerenyi *et al*. 2000; Hidvegi *et al*. 2001; Lidfeldt *et al*. 2003) and in those doing more menial jobs (Brunner *et al*. 1997). Coronary-prone behaviours such as hostility may to some extent explain social-class differences in health. Large population studies have observed the highest levels of hostility among individuals in the lower social classes, especially in older subjects (Barefoot *et al*. 1991; Niaura *et al*. 2000). Meanwhile, these findings may reflect a greater extent of social stress being experienced by individuals who are socio-economically disadvantaged.

The social environment in which the individual interacts is also likely to have consequences for health and psychological well-being, and subsequent development of MS. Individuals who lack social support and/or those who are socially isolated are more likely to develop MS, irrespective of social status (Woodall & Matthews, 1993; Horsten *et al.* 1999; Bjorntorp, 2000; Feldman & Steptoe, 2003). Social support, therefore, may mediate any adverse effect of social circumstances.

Whether psychological and social factors are an antecedent or a consequence of ill health, however, remains to be established. Psychological distress, social circumstances and lifestyle are likely to interact to increase the risk of MS. Adverse social conditions may lead to or be brought about by unhealthy lifestyle practices. It is possible that a tendency towards hostility and anger, as well as disadvantaged social circumstances, may lead to and/or are triggered by detrimental lifestyle practices. Unhealthy lifestyle practices and adverse social environments may therefore elicit negative psychological responses and/or vice versa in susceptible individuals to bring about MS. Implying different pathways to MS, a study that has compared elderly caregivers with similar non-caregivers has found a direct link between psychological distress and MS, in addition to one mediated by lifestyle (Vitaliano *et al.* 2002). It was concluded that stress is exacerbated by lack of social support and/or poor coping skills. Negative psychological traits and states may thus bring about or be brought about by unhealthy lifestyle practices and/or adverse social circumstances.

How does psycho-social stress lead to the development of metabolic syndrome?

The specific nature and scope of different relevant psychological and physiological mechanisms and how they bring about MS is currently unknown (Muldoon *et al.* 2004). Those individuals with a type A behaviour pattern typically respond to laboratory-generated challenges with exaggerated sympathetic nervous system reactivity (Diamond, 1982; Puttonen *et al.* 2003), implying that such individuals may be particularly prone to suffer stress. Chronic stress has been shown to be associated with visceral obesity and MS (Bjorntorp, 1999; Bjorntorp & Rosmond, 1999; Brunner *et al.* 2002; Vitaliano *et al.* 2002; Steptoe & Marmot, 2003). To explain how this association could occur, it is suggested that MS may be the result of a stress-induced cortisol-mediated acute inflammatory immune response (Kiecolt-Glaser *et al.* 2002; Black, 2003; Seematter *et al.* 2004). Chronic inflammation has been associated with CVD and type 2 diabetes (and also periodontal disease and arthritis). The finding that depression and anxiety both appear to have the ability to trigger the release of pro-inflammatory cytokines (proteins that are normally released and signal to other cells in response to infection or injury) provides some support for this argument (Kiecolt-Glaser *et al.* 2002).

The cortisol hypothesis

Cushing's disease, which is the result of increased adrenal secretion of corticosteroids, is often referred to in evidence for the involvement of cortisol in the development of MS. Similar to MS, Cushing's disease is characterised by visceral fat deposition, hypertension, hyperlipidaemia, depression and hypercortisolaemia (Bjorntorp, 2000; Brown *et al.* 2004). There is further evidence to support the involvement of cortisol in the development of MS. Individuals treated with steroids tend to put on weight (Bjorntorp, 2000). Also, there are associations between high salivary cortisol and anthropometric (Wallerius *et al.* 2003; Ward *et al.* 2004) and other measures of MS, such as blood pressure and lipid profile (Rosmond *et al.* 2000), which are consistently observed in older men. Metabolic response to stress is, however, likely to be dependent on both the sympathetic nervous system (flight and fight response) and the hypothalamic–pituitary–adrenal axis (defeat response) (Bjorntorp, 2000). According to this view, stress that is induced by adverse social conditions may trigger neuroendocrine change in two possible ways: first, through the release of the catecholamine neurotransmitters adrenaline and noradrenaline, both of which can bring about an increase in blood pressure in response to sympathetic nervous system activity. Whereas both adrenaline and noradrenaline bring about peripheral vasodilation to enable anxiety and flight, noradrenaline alone brings about peripheral vasoconstriction to enable anger and fight (Diamond, 1982); second, stress-induced hypothalamic arousal is specifically thought to activate adrenocortisol secretion, thereby bringing about increased fat deposit and MS (Brindley, 1995; Bjorntorp & Rosmond, 2000; Drapeau *et al.* 2003). Hypothalamic–pituitary–adrenal axis activity is controlled through negative feedback from glucocorticoid receptors in the hippocampus area of the brain, which are believed to homeostatically control blood pressure and insulin and glucose levels, in response to stressors. Chronic activation of the hypothalamic–pituitary–adrenal axis may eventually impair this negative feedback system (Bjorntorp, 2000). This mechanism may be reciprocal, given that sympathetic nervous system activity is increased by eating and decreased by fasting (Bjorntorp, 2000). Visceral fat, in turn, may release cytokines, which stimulate hypothalamic activity to further increase stress (Drapeau *et al.* 2003). In keeping with this idea, high levels of noradrenaline have been associated with the release of leptin (Eikelis *et al.* 2004). Leptin is an adipocyte hormone that appears to be released in greater quantities in obese individuals (Oppert *et al.* 1997). Leptin is released from fat and is believed to signal other neurochemicals, including the catecholamines, to become active in the central nervous system (Halford, 2001). Thus, it is possible that leptin stimulates sympathetic nervous system activity (Esler *et al.* 2001) to mediate glucose and fat metabolism (Nonogaki, 2000).

The serotonin hypothesis

Links between abdominal obesity and depression suggest dysregulation of serotonin activity that could potentially predispose certain individuals to MS. Further evidence for a role for serotonin in the development of MS comes from studies that have observed response to serotonin agonists. Despite some evidence to suggest that serotonin agonists

(including the commonly-prescribed selective serotonin re-uptake inhibitors) can curb hunger and reduce body weight in the short term (Sargent *et al*. 1997), prolonged use of such drugs seems to induce MS (Baptista, 1999; Zimmermann *et al*. 2003; Almeras *et al*. 2004; Basu *et al*. 2004; Vieta, 2004). Both animal (Roy *et al*. 2004) and human research (Eikelis *et al*. 2004) has implied that enhanced serotonin turnover could be linked to the development of obesity. Amphetamine-like anorexic drugs such as fenfluramine and dexfenfluramine are thought to act by inhibiting re-uptake of serotonin at the central nervous system synapse, thereby enhancing and prolonging its action (Wellman *et al*. 2003). In speculating how enhanced serotonin activity might bring about obesity, it has been suggested that serotonin interplays with leptin and cortisol in producing stress-induced body-weight gain. Intravenous administration of a selective serotonin re-uptake inhibiter has been shown to increase plasma leptin levels and cortisol response to a greater extent in obese women than normal-weight women (Oppert *et al*. 1997). Serotonin activity has not only been implicated in the development of visceral fat but also in the development of other metabolic factors associated with MS. Elevated triacyl-glycerols, hypertension and insulin resistance have been found to be associated with lowered fenfluramine-released prolactin response (a proxy for serotonergic activity), providing further evidence for enhanced serotonin activity in the development of MS (Muldoon *et al*. 2004). There is, therefore, good reason for presuming that serotonin has a role in the psychology of obesity and MS. The notion that metabolic change could be serotonin mediated implies the usefulness of undertaking further research to explore the importance of psychological factors assumed to be linked to enhanced serotonin activity in relation to visceral obesity and MS.

Can risk for metabolic syndrome be predicted from anthropometric measures alone?

Large population research as part of the EU-funded LIPGENE Integrated Project will explore a novel range of potential psychological triggers of MS. A quick easily-assessed non-invasive marker of MS will be required for this purpose. Clinical characteristics of MS such as mid-section obesity, high blood pressure, cholesterolaemia and insulin resistance appear to be both collectively and individually predictive of cardiovascular risk (Lawlor *et al*. 2004). Clinical features indicative of MS appear to vary in how well they predict each other and consequent risk for MS. Anthropometric assessment may provide a more stable indicator of MS over a period of time than biochemical measures (Katzmarzyk *et al*. 2001). Body fat composition, independently of other factors, has been shown to provide a reliable marker of MS through the life course (Yarbrough *et al*. 1998; Vanhala *et al*. 1999; Chen *et al*. 2000) and across cultures (Okosun *et al*. 1998; Martins & Marinho, 2003). The finding that inter-correlations between the different clinical features of MS become closer with age only in individuals who are obese (Chen *et al*. 2000) suggests that obesity may indeed be the

'defining feature' of MS (Gigolini *et al*. 1995). The notion that MS can be inferred from knowledge of non-invasive anthropometric factors alone is therefore feasible.

The task becomes less straightforward when the specific anthropometric factors to use are considered. Perhaps the best evidence comes from studies that have used computed tomography scanning to check visceral adiposity against other features of MS. Such studies have indicated that sagittal diameter provides a reliable indicator of blood pressure, lipid profile and insulin resistance in men, which is more closely correlated with factors associated with MS than either waist circumference, waist : hip ratio or BMI in males (Bjorntorp, 2000; Riserus *et al*. 2004). Of the anthropometric measures, sagittal diameter correlates most closely with visceral fat (Onat *et al*. 2004). As there is a lack of studies that have assessed the value of sagittal diameter in women and because sagittal diameter is difficult and time-consuming to assess, the method remains unsuitable for use in a large group of individuals.

The extent to which BMI and waist : hip ratio predict clinical features that comprise MS appears to be gender dependent (Ho *et al*. 2001; Siani *et al*. 2002; Benetou *et al*. 2004; Onat *et al*. 2004). When all anthropometric measures are considered, waist circumference appears to provide the most convenient and reliable anthropometric marker of clustering of clinical features of MS across gender (Okosun *et al*. 1998, 2000; Siani *et al*. 2002; Snijder *et al*. 2004). There may also be regional differences in terms of which anthropometric measures most accurately reflect metabolic change. A recent study carried out in Portugal has found waist : hip ratio to be a better predictor of MS than waist measures alone (Martins & Marinho, 2003). Both waist : hip ratio and waist circumference will together provide viable and consistent proxy indication of visceral obesity and MS for the purpose of the LIPGENE study.

Conclusions

The LIPGENE study will consider, in a large sample of >50-year-old Europeans (*n* 1500), a novel range of psychological and behavioural traits reflecting activity of various neurochemicals, certain lifestyle, social and demo-graphic factors, and cultural differences therein against anthropometric markers of MS. It will attempt to unravel the relative contribution of each of these factors to the aetiology of MS using multivariate and predictive techniques. The analysis will not only seek to determine causative relationships between variables, but also to identify different constellations of traits and behaviours that underpin MS and may represent separate pathways to CHD and/or type 2 diabetes. The research will also be unique in exploring cross-cultural differences in how psychological factors may bring about obesity and MS. The research also meets a need for a more holistic approach to understanding the psychological and be-havioural underpinning and outcomes of MS.

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