Abstract

Managing diabetes requires dealing with diet, medications, and self-monitoring, besides other pressures of daily living. It, therefore, requires collaboration among individuals with diabetes, their families, and significant others including the social milieu in which they reside. Psychological stress plays a critical role in the cause and course of diabetes, particularly in mastering various self-management skills, which are essential for adequate management of diabetes. It is possible to measure and to resolve such stressors. Besides the patient and the family, the built environment in which the person occupies must be conducive for healthy living. This is a key component in providing an appropriate physical and psychosocial environment. Lacunae in any of the built environmental parameters compromise social and psychological well-being. Psychiatric conditions are also common in diabetes. Both depression and distress are bi-directionally associated with diabetes. The presence of one condition increases the risk of developing the other. In addition, medications used for the treatment of psychiatric conditions have adverse effects on body weight and insulin sensitivity. One must carefully weigh the risk and benefit of the drug class with potential adverse effects. Therefore, identification and management of psychological and psychiatric aspects in subjects with diabetes is an integral and critical component in treating subjects with diabetes.

Keywords: Built environment, circadian, counseling, depression, distress

On Psychology and Psychiatry in Diabetes

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INTRODUCTION

Psychology and diabetes have had a long association. More than 400 years ago, diabetes was postulated to be precipitated by sorrow.[1] Early attempts at linking the two tried to identify personality traits that led to diabetes until it was realized that there was no specific psychological traits predisposing to diabetes.

In general, health was conceptualized on a biomedical model, with a focus only on biological factors. In the management of lifestyle diseases such as diabetes, one must consider other aspects of living such as psychological, social, and environmental, expanding the scope to a biopsychosocial model.

The content of this presentation is based primarily on the work carried out by us; relevant studies published later were cited to give context by clarifying or amplifying our work.

Our early steps into the study of psychology and diabetes

The initial endeavours to studying the psychological aspects of diabetes began with a literature review of the role of hormones in behavior.[2] An invitation to speak at a Psychology conference led to an analysis of the pattern of sexual dysfunction in men with diabetes from the database at our center. It was shown that sexual dysfunction was reported by men who had diabetes for a short duration, suggesting that psychological stress could be playing a role.[3]

While analyzing data in our prospective endocrine database, we recognized that subjects with diabetes comprised the majority. We presented a cross-sectional study on the prevalence of sleep disorders in subjects with diabetes; later we published a case–control study, showing that nearly one-third had sleep disturbances.[4]

These early studies preceded the concept of circadian misalignment with the risk of metabolic and cardiovascular diseases.[5]
BACKGROUND

Psychology plays a role even before diabetes is diagnosed: some individuals put off testing themselves until they are certain they can face up to being diagnosed with diabetes. A series of reactions follow the diagnosis of a life-long condition, which can only be managed but not ‘cured.’ Denial is often followed by anger, guilt, depression, and resolution. The different phases may overlap, and the time to resolution may vary.

Cultural issues may also color how societies deal with disease: for example in developing countries, more emphasis is laid on how the individual feels, with an ability to continue maintaining the routine; less importance is given to dealing with laboratory test results, concepts with which the subjects may not be familiar. Certain populations may not have negative connotations about the disease. This helps in utilizing this neutral base to tailor health promotion on attitudes and behaviors.

Would advice based on personalized risk using both genetics and risk factors help in changing the behavior? Common sense suggests that information about one’s risk of developing a disease would encourage an individual to take preventive measures. Godino et al. studied the effect of communicating genetic or phenotypic risk estimates of type 2 diabetes mellitus. Healthy middle-aged Finnish subjects (n: 569) were advised about lifestyle alone (n: 190) or combined with a risk-based on the genetic score (n: 189) or phenotypic score (n: 190). At the end of eight weeks, groups who were advised with both phenotype and genotype risk did not increase their physical activity in efforts to prevent or postpone diabetes; on the positive side there was no change in anxiety or worry. Evidently the mere availability of information alone is unlikely to alter the behavior of persons at risk. A more comprehensive approach is required: to facilitate behavior change based on genetic testing, provision of recommendations in a way that can be acted upon was more likely to lead to changes in behavior that reduce the risks.

Role of psychological support in the management of diabetes

The management team in diabetes requires support in the psychological sphere. While technology exists for newer methods of treatment, successful implementation requires the individual’s continual self-management behaviors. Behavioural and psychosocial support approaches that are helpful in self-management include ‘problem-solving, cognitive-behavioral, motivational interviewing, family-based approaches, and technology-assisted behavioral approaches’. The role of psychologists is not limited to delivering care alone, but also in giving directions on tailored approaches in prevention and treatment. One must consider the developmental stage of the individual as well as the social support networks that are available. Healthcare and preventive behavior encompass cultural values, beliefs, and health literacy.

Psychological measures employed in diabetes management

The development of psychological measures via questionnaires requires theoretical background knowledge, data collection, analysis, and interpretation. As a representation, the development of ‘The Diabetes Intention, Attitude, and Behavior Questionnaire’ began with the theoretical framework of questions based on the Theory of Planned Behavior. The questions to be included were obtained using information from published literature, with inputs from health professionals along with qualitative findings. A pilot study was carried out, before following up on a larger sample. A confirmatory factor analysis was performed in addition to estimates of floor and ceiling effect; this in turn was followed by evidence for internal consistency, test–retest reliability, and construct validity.

A variety of diabetes-specific questionnaires are available for clinical use. The quality of life questionnaire, originally developed for use in the Diabetes Control and Complications Trial (DCCT) evaluates the worries, satisfaction, and impact related to the treatment of diabetes. It has been used in both type 1 and type 2 diabetes. A related questionnaire, an audit of diabetes-dependent quality of life (ADDQoL) was constructed based on the patients’ perception of the importance of various life aspects, and how each is affected, either positively or negatively. Quality of life questionnaires identify treatments that reduce the burden of diabetes.

The Diabetes Well-Being questionnaire was designed to distinguish symptoms related to diabetes from symptoms of depression. Now designated the WHO Bradley well-being questionnaire, it has four subscales: anxiety, energy, depression, positive well-being, and can identify incremental benefits to treatments.

Diabetes treatment satisfaction questionnaire measures satisfaction with the treatment regimen. It is not designed to measure satisfaction with other service aspects of care. This can be used to improve the patient’s quality of life.

Other psychological scales include psychological adjustment to diabetes, diabetes-specific health beliefs, perceived control of diabetes, and barriers to self-care. Recently, a 19-item diabetes stigma-assessment scale was developed to measure perceived and experienced stigma with type 2 diabetes.

It is important to look at outcomes of psychological measures along with other clinical and laboratory parameters.

Application of psychological measures in the clinical management of diabetes

Quality of life is affected in the presence of diabetic vascular
disease. Monitoring by a nurse specialist improved quality of life, independent of metabolic control – which one must be vigilant about and ensure that psychological improvement occurs in tandem with improvement in metabolic control. The presence of sleep disturbances and symptomatic complications such as painful neuropathy adversely affects the quality of life. Treatment can be fine-tuned based on the quality of life indices, taking care to match patient satisfaction with metabolic parameters. Similarly one must not offer inappropriate hope or interventions.

**Psychological issues in diabetes**

Considering that the patient along with the family form the unit of diabetes self-care, it is necessary to identify psychosocial problems and to overcome them. Self-care entails balancing medications, diet intake, energy expenditure, and lifestyle modifications after the diagnosis of diabetes. Supportive social and environmental factors may not always be available for those who truly need them: e.g., poor patients, who are stressed and those with distressful conditions. Not only will these worsen glycemic control, but lack of support interferes with self-care behavior leading to a descending spiral.

**Association of psychological stress in the onset of diabetes**

Stress could play a pathogenic role in the onset as well as the natural history of diabetes. Perceived neighborhood stress influences the degree of obesity. In the same way, perceived social stress could also be responsible for the onset of type 2 diabetes mellitus. Other stressors such as recent adverse life events, emotional stress, anger, hostility, and work stress could also contribute to the onset of diabetes mellitus. Bjorntop originally postulated that stress results in activation of the adreno-corticotropin-cortisol axis, ultimately leading to metabolic abnormalities and accumulation of abdominal fat. The hypothesis was validated by the Hoorne Study and by The Multi-Ethnic Study of Atherosclerosis (MESA).

McEwen postulated the concept of allostatic load to explain the role of the hippocampal region in the brain which has receptors for stress hormones in perceiving and responding to stress. Acute stress response is life-saving in the short term with activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. During chronic stress, with attendant mild elevation of cortisol levels and prolonged activation of the sympathetic nervous system results in visceral fat deposition leading to central obesity and type 2 diabetes mellitus.

Although there is no consistent elevation of plasma cortisol in obesity, the diurnal variation appears to be disturbed, along with increased peripheral metabolism of cortisol. Activation of HPA or generalized changes in the sensitivity of tissues to corticosteroids by themselves may not lead to central obesity. Seckl postulated that increased peripheral clearance of cortisol could activate compensatory activation of the HPA axis, resulting in hyperresponsivity of the adrenal gland to stress stimuli.

Another player in the HPA axis is the 11 beta hydroxysteroid dehydrogenase, which catalyzes the conversion of inert cortisone to active glucocorticoids, thus acting as an amplifier for cortisol action at a local level. Selective elevation of the enzyme level in adipose tissue could lead to adverse metabolic effects.

There is evidence that altered follicular stimulating hormone (FSH) levels could act as a mediator of metabolic syndrome. Stefanska et al. showed that low levels of FSH are associated with increased risk of metabolic abnormalities in postmenopausal women. The possible reasons are, the higher estrogen in obese postmenopausal women leading to aromatization of androgens to estrogens in adipose tissue, which suppresses FSH secretion. In addition, other compounds such as follistatin and activin may influence the FSH level and simultaneously regulate insulin sensitivity and chronic inflammatory status.

**Family support in the management of diabetes**

It is now recognized that self-management of diabetes requires support from the family. A number of behavioral regulations are required based on well-known theories such as interpersonal theory and self-determination theory. The interpersonal theory proposes that transactions are promoted by behaviors that are “high affiliation (warm, friendly) but derailed by hostility and dominance.” The self-determination theory predicts that autonomous behavior is regulated by three basic needs: connectedness, competence, and autonomy.

In adulthood, subjects with diabetes must cope with long-term complications. They often have to depend on the spouse who could no longer be in good health. The involvement of the family and the spouse may either help or hinder the management of diabetes: active support in diabetes care is helpful while nagging and criticism have the opposite effect.

In our studies of adults with diabetes, we showed that in general, women had greater distress than men. Younger subjects under the age of 40 had a better quality of life and better satisfaction with the management of diabetes; integration of diabetes and coping were better in men. There was a positive correlation between the “chance dimension of locus of control” and exercise, diet, and glucose testing. Both their spouses and children considered that a diagnosis of diabetes did not make the subject with diabetes abnormal. It did not adversely affect their relations; interestingly, more than 85% were knowledgeable about the disease, and the positive attitude could not be attributed to ignorance.

More men had the support of spouse in following dietary regimen; more women depended on their spouse for engaging in physical exercise. Concerns about the disease were mostly shared with the spouse.

In the follow-up phase of the study, we observed that there was a significant drop in attendance toward the end of the study. Interestingly, subjects who made only one visit received greater spousal emotional and other forms of support when
having to deal with stress due to diabetes. This highlights the importance of support from the health care team when it was lacking in the family unit.

**Translation of principles to practice**

There is ample evidence that risk factors leading to obesity, insulin resistance, and diabetes can be modified to postpone, if not prevent the onset of diabetes. Even subjects with diabetes often do not follow health measures such as physical exercise or smoking cessation.[47]

The built environment is the term given for “environments that are modified by humans, including homes, schools, workplaces, highways, urban sprawl, accessibility to amenities, leisure and pollution.”[48] Epidemiological studies showed that men living in cities were more likely to be obese than those living in suburban areas, indicating that neighborhoods could influence physical activity.[69]

To understand the complex interactions of the built environment, it is necessary to identify how it can be modified to affect the behavior of its inhabitants. In a pilot study, we examined selected components of the built environment to understand its relation with body weight.[50] The following variables were related to higher body mass index: those who were staying at home, who were moderately active physically, and those who did not report taking an afternoon siesta. These are in consonance with recognized risk factors for overweight and obesity: lack of physical exercise and compromised sleep. The last factor (namely those who did not have afternoon siesta) at first appeared to be a chance occurrence; however, studies published shortly afterward have shown a clear association of napping and the risk of diabetes in both cross-sectional[53] and longitudinal[52] studies. The mechanism is yet to be understood.

Sleep and circadian rhythm are increasingly recognized to play pivotal roles in a variety of metabolic disorders.[54] In a meta-analysis linking the risk of type 2 diabetes mellitus with the duration of sleep (n: 482,502), Shan et al. reported that the lowest risk of diabetes was observed in individuals who slept between seven and eight hours a day. The pooled relative risk for diabetes was 1.09 for each hour of shorter sleep.

The relation between sleep and glucose metabolism is multifactorial: lowered glucose utilization when awake, overactive sympathetic nervous system, imbalance of growth hormone, HPA system, systemic inflammation, obstructive sleep apnea, and altered levels of appetite-regulating hormones such as leptin and ghrelin.[55]

Built environment influences sleep, relaxation, and access to food. Studies in the west have shown that availability of unhealthy or junk food contributes significantly to obesity and risk of metabolic syndrome; a recent study has replicated the findings in New Delhi where adolescents tended to eat lesser portions of healthy foods, and instead preferred to consume junk food and carbonated drinks.[56] This underlines that built environment factors must enable access to healthy food choices.

**Psychosocial measures to ensure treatment compliance**

Diabetes, described as a “complex and burdensome disease,” requires many decisions to be made in terms of food, medicines, and physical exercise.[57] Self-management training must be offered, along with ongoing support to maintain the goals that were provided in education.

Concerns in three broad areas must be addressed: general, psychological, and social.[54] General aspects include creating awareness among the public, appropriate communication between the healthcare provider and the patient; psychological and psychiatric assessment of the patient, with identification and removal of barriers; social issues such as family structure, gender discrimination, culture, and religious beliefs.[58]

A number of behavior interventions have been employed in promoting diabetes management. The underlying basis included social cognitive theory, family systems theory and social-ecological model.[59] Robust evidence exists for the efficacy of cognitive behavior therapy,[60] motivational interviewing,[61] and information-motivation-behavioral skills model of self-care.[62] Innovative methods are being introduced such as being kind to oneself, in not being too self-critical for true or perceived transgressions in diabetes management.[63] Ethnic-specific intervention programs must be employed.[64]

**Importance of social support**

The importance of social support has been brought to the fore in aiding self-management of diabetes. Not just the immediate family,[65] but social conditions affecting the family also have an influence.[66] Increasing health care costs in the absence of proportionate improvement of health outcomes have led to the realization that alone, medical care cannot improve overall health without addressing where and how people live.[67] One must consider personal behavior and medical care, along with living and working conditions in homes and in the community. These ultimately depend on the economic and social opportunities and resources that are available.[67]

The interdependence of all these factors are being studied by showing the effects on gene expression that can influence proinflammatory responses.[68]

Social support is defined as “help provided by family, friends, neighbours, or others and includes different domains, such as information, emotional comfort, and practical help.”[69] Better self-management ability was related to networks supporting information, emotional needs, and attendance to community organizations.[69]

On a broader scale, macroeconomic factors related to social support influence health via inequality of income and of economic shocks.[70] Health disparities operate at different pathways such as health behaviors, stress hormones, and the perception of stress based on the social hierarchy.[71,72]

An integrated theoretical model was developed to identify which aspect of social support was more effective in improving self-management of diabetes. Informational support was most important, followed by tangible support and emotional support.[73] The overarching goal of all these efforts is to
understand how these interactions give insights into improving metabolic control and thereby reduce complications.[72] Shao et al. have shown how social support can improve outcomes of managing diabetes: social support improves self-motivation, leading to improved compliance to self-management thereby resulting in better metabolic control.[74] Purists try to differentiate “medicalization” of sociology and lifestyle that provides “medically accepted scientific evidence to support longstanding sociological arguments.”[75] In contrast to the concept of lifestyle as understood by mainstream sociological thought, where people who become unwell are overtly or covertly blamed for being responsible for their ill-health employing a moralistic and discriminatory approach.[76]

Psychiatric conditions and diabetes
The difference between psychological conditions and psychiatric conditions can be considered as being qualitative. There is increasing evidence for the occurrence of depression,[77] subclinical depression,[78] anxiety,[79] and eating disorders[80] in diabetes.

Diabetes and psychiatric disorders being common in populations, the difference in presentation for care may depend on the perception about the condition in the people and the social milieu; in addition, one must tease the directionality of the twin conditions, viz whether they occur independently of each other because they are both common, or whether the occurrence of one increases the risk of another.[81] Whereas depression is the most common and most studied co-morbidity in diabetes, other conditions also co-exist, namely anxiety disorders, eating disorders, and schizophrenia to a lesser extent.[82,83] Other than affecting physical health, psychiatric conditions have economic, public health, and humanitarian costs.[84] In the Baltimore Epidemiologic Catchment Area Study, anxiety disorders were not associated with increased risk of developing type 2 diabetes or of increased prevalence of complications among those with diabetes.[85] However, pathological anxiety measured by the Hamilton Anxiety Rating Scale is reported to occur during the course of type 2 diabetes mellitus.[86] This may be more prominent in specific subgroups, such as women with increased duration of diabetes who are on insulin treatment.[87]

A recent meta-analysis of studies from India studying the prevalence of depression among subjects with type 2 diabetes mellitus (n: 10,270) showed that nearly a third had depression (38%; CI: 31%–45%).[88] It was more common among those with complications of diabetes. Jin et al. have developed a multilevel regression model to predict depression in diabetes. Patient Health Questionnaire-9 (PHQ-9) score was used to assess depression; from 29 factors, predictors were selected to make population average predictions as well as for individual patients. The variables were selected from the previous diagnosis of major depressive disorder, age at baseline, diabetes emotional burden, diabetes regimen distress, number of ICD-9 diagnoses, self-rated health, employment status.[89] In a follow-up study of type 2 diabetes, screening for depression and anxiety, both lifetime and current, was suggested for achieving better health outcomes.[90]

Role of drugs used in psychiatric disorders
Antipsychotic drugs are used to treat bipolar disorder, schizophrenia, and related conditions. Typical or conventional antipsychotic drugs such as chlorpromazine, thioridazine, and haloperidol though effective, induce adverse effects; in contrast, the “atypical” agents such as clozapine, risperidone, olanzapine, and ziprasidone have a better neurological adverse effect profile and better clinical efficacy.[80] However the atypical drugs are limited by their adverse metabolic profile: they induce weight gain ranging from 0.43–4.5 in the short-term, induce insulin resistance and lead to hyperlipidemia.[81] Weight gain results from directly stimulating appetite or by endocrine effects such as hyperprolactinemia, hypercortisolism, and lowered level of gonadal steroids.

Weight gain is seen with the use of antipsychotic agents clozapine, olanzapine, quetiapine, risperidone, mood stabilizers such as valproic acid derivatives, lithium, antidepressants such as mitrazapine, tricyclic antidepressants, monoamine oxidase inhibitors and others, except bupropion. Hypertriglyceridemia is particularly seen with the use of clozapine and olanzapine. Valproic acid derivatives, carbamazepine, mirtazapine, and selective serotonin reuptake inhibitors (SSRIs) are associated with dyslipidemia. Insulin resistance and diabetes mellitus can be induced by clozapine, olanzapine, valproic acid derivatives, and tricyclic antidepressants.[91]

The newer atypical antipsychotics could alter the gut microbiome leading to inflammation and suppression of metabolic rate, all contributing to weight gain and metabolic complications.[92] Kowalchuk et al. postulated that antipsychotic drugs could directly influence glucose metabolism without inducing weight gain. Potential mechanisms include antagonism of neurotransmitters that are responsible for their antipsychotic effect.[93] It is possible that genes involved in regulating food intake via central mechanisms, along with gut microbiota could contribute to weight gain and metabolic syndrome.[94]

Management of drug-induced metabolic side effects is not different in diabetes. Careful choice of an antidepressant drug must balance the efficacy of its primary effect and the adverse metabolic abnormalities. Other measures include calorie restriction and physical exercise.[81] Cognitive behavioral therapy was effective for reducing weight gain in subjects using antipsychotic agents.[95]

Other innovative approaches: Stress
Considering that stress could play a role in the initiation and management of diabetes, stress relief relaxation, and related responses can be used. Methods that align the mind and body include breathing techniques, progressive muscle relaxation, guided imagery, meditation, biofeedback, and yoga.[96]

Yoga has for long been studied in diabetes mellitus. Sahay et al. performed early studies on the beneficial effects of yoga on metabolic parameters.[97] It could be employed to reduce...
the risk of diabetes mellitus and to lower cardiometabolic risk factors.[90] Similarly a 40-day practice of yoga was shown to improve psychological well-being, reduce anxiety, and lower body mass index.[99]

Spirituality religion and prayer can also aid in the relief of stress.[100] Yoga and other techniques could act by stabilizing the autonomic nervous system and regulating the HPA axis.[101] These may bring about a change in gene expression[102] and changes in transcriptome to improve mitochondrial energy production and utilization.[103] A recent review concluded that mind–body interventions downregulate the genes involved in the nuclear factor kappa B pathway, thereby countering the effects of chronic stress to lower the risk of inflammation-related diseases.[104]

**Other innovative approaches: Managing diabetes and depression**

Diabetes and depression often occur together, and both must be simultaneously managed; the problem boils down to a lack of qualified mental health care professionals. To bridge the gap, an innovative study was carried out called The INtegrating DEPrEssioN and Diabetes treatmENT (INDEPENDENT) Study. The aim was to assess whether depression as assessed by the PHQ-9 screening instrument can be managed by trained but nonprofessional psychiatrists by coordinating with the family and the healthcare team comprising, the primary physician, specialist endocrinologists/diabetologists and psychiatrists. The four sites in India were: Madras Diabetes Research Foundation, Dr. Mohan’s Diabetes Specialities Centre, Chennai, Department of Endocrinology, AIIMS, New Delhi, Endocrine and Diabetes Centre, Visakhapatnam, Diacon Hospital, Bangalore.

It was a longitudinal study assessing whether improvement of depression is associated with improved metabolic parameters and whether they would persist over time.[105] Funded by NIDDK NIH HHS, it was done in collaboration with Emory University, Georgia, University of Washington, Seattle (names of collaborators given in the references).

The unique aspect was the involvement of a team approach for management, and adaptation of methods based on published literature which were fine-tuned to qualitative interviews with subjects having diabetes and their significant others.[106] The results of this important trial are bound to help in translating science to patient care. Leveraging the help of a care-coordinator who acts as a bridge between the patient and the healthcare team, the outcomes of both diabetes and depression can be improved.

**Conclusions**

Diabetes is a chronic lifestyle condition, which demands self management for optimal outcome. Psychological, social, and psychiatric issues are bound to come up considering the network of interactions. The healthcare team must be trained and prepared to deal with all these aspects on a continual basis. Physicians taking care of subjects with diabetes must anticipate, identify, and manage the psychological and psychiatric issues that may appear during treatment. This is particularly important when the diagnosis of diabetes is first made. Being aware of the initial reactions and that they are likely to resolve over time, and allaying the anxiety are essential skills for the physician. In addition, depression, a common co-morbidity must be identified. If it is mild to moderate, the physician may start antidepressant drug therapy and carefully follow the clinical response. Severe depression with suicidal thoughts requires immediate referral to a psychiatrist for treatment. Such coordinated care encompassing physical, metabolic, psychosocial, and psychiatric aspects can translate the evidence obtained from clinical trials to clinical practice.[107] The recently published INDEPENDENT study showed that Indian subjects with diabetes and depression showed improved in both with a collaborative care intervention for 12 months: importantly, there was improvement in the composite measure of depressive symptoms and cardiometabolic parameters even 12 months at the end of active intervention.[108] This is the first demonstration of such an outcome without the primary involvement of a specialist in psychiatry. It shows the potential of trained non-specialist staff to coordinate and counsel for improvement of depressive symptoms and of metabolic control. There is evidence for common pathogenic links between insulin resistance and cognitive decline that can lead to associated psychiatric symptoms.[109] In addition, it is possible to employ deep learning and artificial intelligence to predict the occurrence of psychological distress.[109] A confluence of social science, medical science and big data should improve the outcomes of diabetes management.

**Living effectively with diabetes**

- Women must learn to adopt a positive attitude to diabetes and its management and make adjustments in dealing with it along with the help of family
- Psychological well-being in the elderly is important; depression and anxiety also tend to be more common
- Both men and women must develop a positive approach to managing diabetes
- Effective self-management entails interactions among the patient, family, social support, and built environment
- Methods are available to identify and treat psychological stress and psychiatric conditions such as depression.

*Adapted from Ref 44.

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