

Comparative efficacy of agomelatine versus sertraline in major depressive disorder in Himalayan region of India

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ABSTRACT

Background: Depression, a major common affective disorder which carries excess mortality through suicide. Among various drug classes available SSRI's are usually a choice, but many patients show inadequate response, residual symptoms or discontinue medication due to intolerable side effects. Disturbances of circadian rhythm function are an etiopathogenic hallmark of depression. The degree of circadian misalignment correlates with the severity of depression and circadian abnormalities may partially be a consequence of alterations in behavior and sleep patterns that accompany depression. Agomelatine an agonist acts on MT1 and MT2 receptors and antagonist of 5HT_{2c} receptors contributes to its resynchronization of circadian rhythms, enhancement of dopaminergic and adrenergic input to the frontal cortex, induction of hippocampal neurogenesis, and ultimately, to its antidepressant effect.

Methods: The study was randomized, prospective, comparative and interventional regarding the efficacy of therapy. Hundred consenting patients of MDD attending psychiatry OPD were screened for possible enrollment into group A (Agomelatine) and group B (Sertraline). Patients were assessed by semi-structured case recording form, DSM-IV-TR Criteria for major depressive episode, Hamilton Rating Scale for Depression (HAM-D) and Clinical Global Impressions for severity (CGI-S) at baseline and CGI for improvement (CGI-I), every two weeks interval and final assessment at 8 weeks.

Results: Socio-demographic parameters like age and sex distribution, marital status, locality, family type, educational status, occupation and socio-economic class were comparable between two groups. Similarly baseline HAM-D and CGI-S values between the two groups were statistically non-significant. HAM-D, CGI-S and CGI-I values at eight weeks among the two groups were also statistically non-significant but in all three sertraline had decreased the values to a greater extent and showed a trend towards improvement.

Conclusions: Both groups had shown significant decrease in scores of all scales i.e. HAM-D, CGI-S, and CGI-I at the end of 8th week as compared to baseline scores, indicating that the uses of agomelatine and sertraline have resulted in significant improvement in symptoms of patients of MDD and reinforcing their efficacy in treatment of MDD. No statistical difference was observed between two groups.

Keywords: Agomelatine, Circadian rhythm, Depression, Sertraline

INTRODUCTION

World Health Organization defines depression as a common mental disorder that presents with depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, decreased sleep or appetite, and poor concentration. Depression is a major

affective disorder, affecting approximately 350 million people worldwide.¹ It is the commonest psychiatric conditions, and third leading cause of disease burden in the general population.^{2,3} Depression not only imposes a great burden upon the health care services, but also results in excess mortality through suicide.⁴ Ethnic and regional variations are present in the manifestations of depression.⁵

The lifetime prevalence of major depression globally ranges from 1.5% to 19%.⁶

Among various treatment options, pharmacotherapy is the most commonly employed modality.⁷ Pharmacogenomics data suggest that genetic make-up of different racial groups vary to some degree, leading to implications on the pharmacokinetics and pharmacodynamics of medications.⁸

Monoamine hypothesis for depression implicates a lack of noradrenaline and serotonin (5-HT), and the receptor hypothesis, which proposes the up-regulation of certain noradrenergic and serotonergic receptors, and their subsequent down-regulation in response to treatment. The two theories are not mutually exclusive, and have arisen from attempts to elucidate the mechanisms of action of serendipitously discovered, as well as more innovative antidepressants.⁹

Most antidepressant agents act by increasing the availability of the monoamines at neuronal synapses, particularly in the locus coeruleus (noradrenaline) and raphe nucleus (serotonin). The pioneering tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) inhibit their reuptake and metabolism, respectively. The more recent antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs) and noradrenaline reuptake inhibitors (NARIs) also act chiefly through these monoaminergic mechanisms. The noradrenaline and dopamine reuptake inhibitor (NDRI), bupropion, is unique since it also increases dopamine neurotransmission, chiefly in the nucleus accumbens and prefrontal cortex.

An alternative approach to the pathogenesis of depression is rooted in circadian biology. Circadian rhythms (CR) include all physiological processes that display a period of 24 hours.¹⁰ The body's circadian system regulates many rhythmic physiological functions, such as the sleep-wake cycle, feeding, thermoregulation, hormone release, and metabolic regulation.¹¹ The CR in mammals is organized hierarchically within the core biological clock or main circadian pacemaker located in the supra-chiasmatic nuclei (SCN) within the anterior hypothalamus, which drives circadian rhythms within and outside of the brain. The rhythms generated by this internal biological clock are continuously entrained via the retina by environmental signals, predominantly by the cycle of light and dark, in addition to internal synchronization.^{12,13} The second main circadian pacemaker is the pineal gland, which synthesizes melatonin.

Circadian function is often disrupted in depression. The internal circadian timekeeping system responds poorly to environmental cues, resulting in phase shifts. Diurnal variations occur earlier (phase advance) or later (phase delay) than in healthy individuals. Patients with depression

often show larger daytime mood variation, disturbances in hypothalamic-pituitary-adrenal (HPA) axis function, more severe cognitive difficulties, and sleep-wake cycle disturbances, which may manifest as delayed onset of sleep, difficulty in maintaining sleep, and early morning awakening. The degree of circadian misalignment correlates with the severity of depression and thus, circadian abnormalities may partially be a consequence of alterations in behavior and sleep patterns that accompany depression.¹⁴⁻¹⁶

Melatonin secretion is regulated by the environmental light/dark cycle via the SCN, with the peak of secretion during the night and almost undetectable levels during the day.¹⁷ It is associated with increased sleep propensity, reduced body temperature, and decreased alertness.^{12,17,18} Melatonin's binding to the SCN has two effects: inhibition of neuronal firing or phase shifts in circadian rhythms.¹⁸ Both melatonergic and serotonergic receptors have been identified in the SCN.

Agomelatine, the first regulatory approved melatonergic antidepressant, is a potent agonist of melatonergic receptors, melatonin 1 (MT1) and melatonin 2 (MT2). Like melatonin, agomelatine acutely and dose-dependently inhibits the firing rate of SCN neurons (MT1) and directly resynchronises and normalises disturbances of circadian rhythm (MT2).¹⁹ Agomelatine also binds to 5HT_{2c} receptors, with lower affinity and acts as an antagonist of these receptors, which contributes to its resynchronisation of circadian rhythms, enhancement of dopaminergic and adrenergic input to the frontal cortex, induction of hippocampal neurogenesis, and ultimately, to its antidepressant effect.¹⁶

Sertraline, a SSRI agent with antidepressant efficacy in MDD as well as in other psychiatric conditions.²⁰ Sertraline is primarily a serotonin reuptake inhibitor with a binding affinity towards the serotonin transporter. Therapeutic doses of sertraline (25-200mg/day) taken for four weeks resulted in 80-90% inhibition of serotonin transporter (SERT) in striatum. Sertraline is slowly absorbed orally, achieving its maximal concentration in the plasma 4-6 hours after ingestion. It is 98.5% plasma protein bound with a half-life of 13-45 hours. It has similar tolerability profile to other SSRIs, common adverse events being diarrhea, nausea, trembling, sexual dysfunction and weight gain. The incidence of diarrhea was higher with sertraline in comparison to other SSRIs, their safety and tolerability profiles remain superior to TCAs and MAOIs.²¹

Many patients show inadequate response, residual symptoms or discontinue medication due to intolerable side effects with current therapies. Hence keeping in view of genetic, environmental and racial factors, effect of agomelatine in this region was required to be planned and studied.

Aims and objectives to compare the efficacy of agomelatine versus sertraline in Major Depressive Disorder.

Study design, randomization and intervention

The present study was conducted on an outpatient basis in the department of Psychiatry at Indira Gandhi Medical College, Shimla from July 2014 till August 2015. The study was randomized, prospective, comparative and interventional regarding the efficacy of the treatment.

A total of hundred patients of MDD attending psychiatric outpatient department, who fulfilled the inclusion and exclusion criteria and who agreed to participate in the study by giving written informed consent were included as cases. Fifty patients received agomelatine (Group-A) and fifty patients received sertraline (Group-B) were enrolled.

After a baseline assessment, patients were randomized to either of the two treatment groups through block randomization technique. Randomization was concealed using sequentially numbered opaque sealed envelope. Blinding was observed between the observer and patient. Patients were randomized to assign agomelatine (Group-A) or to the sertraline (Group-B). Patients assigned to agomelatine initially received 25 mg of the drug OD at bedtime for two weeks and was increased to 50 mg /day in those patients who did not show improvement on 25 mg/day, and those assigned to the sertraline group received 50 mg of the drug OD in the morning. Patients were followed up at 2-weeks interval for 8-weeks. The dose adjustments were done during follow up period depending upon the patient's response. Final assessment was done at the end of 8-weeks.

Inclusion criteria

Patients within the age group of 18-65 years; diagnosis of MDD according to Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition (Text Revision) (DSM-IV-TR) criteria and patient consenting himself or through his legal guardian.²²

Exclusion criteria

Current DSM-IV-TR diagnosis other than MDD, Substance dependence; Clinically significant medical illness; pregnant and lactating women; patients judged to be at high suicidal risk; patients who had received Electro Convulsive Therapy (ECT) within one month before being enrolled; patients who had previously received drug treatment for more than 16 cumulative weeks and history of refractoriness to study drugs.

A detailed history from the patient and/or a reliable person who had known the patient well was taken as per pre-designed recording format. Examination included detailed Mental Status Examination (MSE) besides routine physical examination. Hamilton Rating Scale for

Depression (HAM-D) and Clinical Global Impressions (CGI) scales were applied to assess the severity of depression.^{23,24} Before applying HAM-D and CGI scales to the subjects in the study, training was received by the observer from the consultant psychiatrist, for applying these scales on ten patients with MDD.

Instruments/ tools

- *Case record form:* Self devised, semi-structured proforma.
- *DSM-IV-TR criteria for major Depressive Episode/Disorder:* These criteria attempt to set an operational threshold for depressive disorder based on specified number of items and their temporal patterns.
- *Hamilton Rating Scale for Depression (HAM-D):* A widely used clinician-administered depression assessment scale pertaining to symptoms of depression experienced over the past week.
- *Clinical global impressions:* A widely used brief assessment tools in psychiatry with high face validity.

Investigations

Routine blood investigations like Hb, TLC, DLC, ESR, Blood sugar etc. were carried out. Other relevant investigation like CT Head, Thyroid Function Tests etc. were done as per the need felt.

Clinical follow up

One follows up was done at two weeks, and the drug dosage was adjusted according to the response or side effects by the psychiatrist. It had included history, examination, and application of HAM-D and CGI scales. Relevant investigations were carried out if required. The final assessment was done at the end of eight weeks.

Statistical analysis

Categorical and continuous variables were reported as percentages and mean±standard deviation respectively. The differences in the distribution of categorical variables among study groups were compared by χ^2 test and unpaired students t-test for continuous variable. 2-tailed value of <0.05 was taken as statistically significant.

RESULTS

Of the hundred patients enrolled, four patients left treatment midway on account of little improvement in clinical symptoms (two each in group A and B) while four patients were lost to follow-up (one in group A and three in group B). Ninety two patients completed their follow-up at 8 weeks. The data was analyzed on various socio-demographic factors like age and sex distribution, marital status, locality, family type, educational status, occupation and socio-economic class. Both groups were also

compared with respect to application of HAM-D and CGI scales for severity at baseline and subsequent follow-ups. CGI for improvement was applied at 8 weeks between the two groups.

Age and sex distribution

Age and gender were well matched in both the groups, having mean values for age 40.63±10.75 years versus 39.82±12.79 years, (p>0.74) in the agomelatine and sertraline group, respectively. The mean values for gender (females) was 51.1% versus 66.7, (p>0.13). Majority of the patients (59.5%) and (46.7%) in groups-A and B were in the age group of 36-55 years.

Locality and marital status

Majority of the patients in Group A (63.8%) and Group B (60.0%), (p>0.70), lived in rural areas. Most of the patients likewise in Group A (76.6%) and Group B (80.0%), (p>0.38) were married.

Family type and educational status

Majority of the patients (74.5%) and (73.3%), (p>0.90) lived in a nuclear family in group A and B, while most of the patients (48.9%) and (57.8%), (p>0.23) were graduates in the two groups, respectively. Only one patient (2.1%) was illiterate in the agomelatine group.

Occupation

Majority of the patients (34.0%) and (31.1%), (p>0.76) were businessmen in the two groups, respectively. Only two patients (4.3%) in agomelatine group and one patient (2.2%) in the sertraline group were unemployed (Figure 1).

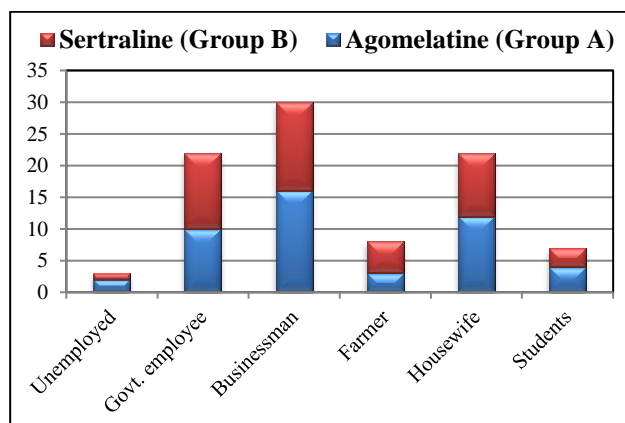


Figure 1: Occupation of patients in the two groups.

Socioeconomic Class (Kuppuswamy’s Socioeconomic Scale)

Most of the patients (53.2%) and (80.0%), (p>0.84) belong to the lower middle class in the two groups, respectively. None of the patients belonged to upper class (Table 1).

Table 1: Socio-economic class of patients between the two groups.

Socioeconomic status: (Kuppuswamy’s scale)	Agomelatine (Group A) (n = 47)	Sertraline (Group B) (n = 45)	P-value
Upper	0 (0.0%)	0 (0.0%)	0.84
Upper middle	9 (19.1%)	9 (20.0%)	
Lower middle	25 (53.2%)	24 (53.3%)	
Upper lower	8 (17.0%)	8 (17.8%)	
Lower	5 (10.6%)	4 (8.9%)	

Hamilton depression rating score and clinical global impression scores

Baseline Hamilton Depression Rating Score (HAM-D)

The mean values of HAM-D score was 24.76±1.90 in the agomelatine group while in the sertraline group it was 25.17±1.77 at baseline, which was statistically non-significant (p>0.28).

Baseline Clinical Global Impression Score for severity (CGI-S)

The mean values of CGI-S score was 4.80±0.74 in agomelatine group while in the sertraline group it was 5.04±0.63 at baseline, which was statistically insignificant (p>0.10).

Clinical Global Impression Score for the improvement at 2-weeks

The mean values of CGI-I score was 3.51±0.54 in agomelatine group while in the sertraline group it was 3.55±0.50 on first visit at 2-weeks, which was statistically non-significant (p>0.68).

Hamilton Depression Rating Score (HAM-D) after 8-weeks

After 8-weeks, the mean values of HAM-D score was 9.51±1.28 in agomelatine group while in the sertraline group it was 9.08±0.97, which was statistically non-significant (p>0.08) but showing a trend towards improvement. Sertraline has decreased the HAM-D score by a large extent in comparison to agomelatine (Figure 2).

Clinical Global Impression Score for severity (CGI-S) after 8-weeks

After 8-weeks, the mean values of CGI-S score was 1.70±0.85 in agomelatine group while in the sertraline group it was 1.55±0.65, which was statistically non-significant (p>0.36) but showing a trend towards improvement. Sertraline has decreased the CGI-S score to a greater extent in comparison to agomelatine (Figure 3).

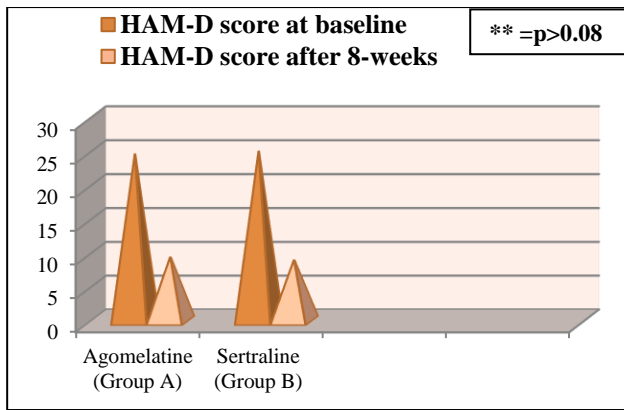


Figure 2: Depicting differences in HAM-D scores at baseline and 8 weeks among the two groups.

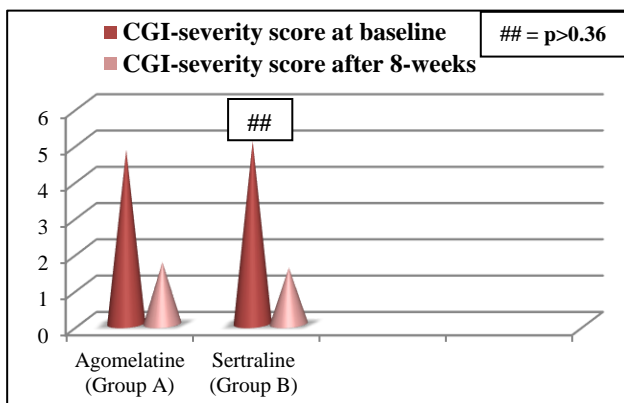


Figure 3: Depicting differences in CGI-S scores at baseline and 8 weeks among the two groups.

Clinical Global Impression Score for the improvement at 8-weeks

After 8-weeks, the mean values of CGI-I score was 1.80 ± 0.77 in agomelatine group while in the sertraline group it was 1.60 ± 0.49 , which was statistically non-significant ($p > 0.12$), but showing a trend towards improvement. Sertraline has decreased the CGI-I score more in comparison to agomelatine (Figure 4).

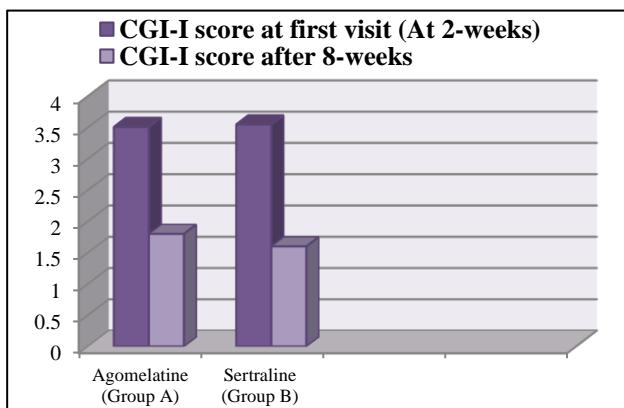


Figure 4: Depicting differences in CGI-I scores at baseline and 8 weeks among the two groups.

DISCUSSION

Depression a major psychiatric condition, has increased prevalence in the 21st century due to life stressors like unemployment, migration to urban areas for better job opportunities, work stress, social detachment, little time for recreation and exercise, and lack of family support system due to the concept of nuclear families. Traditional therapies aimed to increase monoamine levels had myriad of adverse drug events and these along with patient skepticism, social stigma, residual symptoms, concerns of over-addiction and lack of perceived benefit often leads to premature discontinuation of antidepressants causing relapse.²⁵ Approximately 30%-40% of the patients fail to respond to treatment and less than 60% achieve remission.²⁶ Depression treatment guidelines recommend continued drug therapy for 6-12 months following remission of acute symptoms.⁷

Agomelatine a synthetic analogue of melatonin, serves to regulate various circadian rhythms, including sleep-wake cycles.²⁷ Stimulation of MT1 and MT2 receptors has a normalizing effect on disturbed circadian rhythms. Agomelatine also inhibits the activity of serotonin 5HT2C receptor subtypes.¹⁶ Antagonism at the 5HT2C receptor is associated with antidepressant and anti-anxiety activity and also increases slow-wave sleep.²⁸ The pharmacology of agomelatine, with its combined effects at MT1, MT2 and 5HT2C receptors, is therefore unique and distinct compared with other antidepressant drugs.

Treatment in the acute phase of MDD include pharmacotherapy, psychotherapy, a combination of both, or various somatic therapies such as electroconvulsive therapy (ECT), trans-cranial magnetic stimulation, or light therapy. For most patients SSRI or SNRI, mirtazapine, or bupropion is recommended.²⁹ SSRIs and SNRIs are often associated with sleep-disturbing effects that occur mostly in the early stages of treatment; some other antidepressants like amitriptyline or mirtazapine promote sedation, sleep, and daytime drowsiness.³⁰ In patients with depression, sleep usually improves after 3-4 weeks of effective therapy, but this deters patients from using certain drugs.³⁰

Age and sex distribution

Mean of the patients was 40.63 ± 10.75 years in agomelatine group while in the sertraline group it was 39.82 ± 12.79 years. In other studies, mean age of patients ranged from 37.3 to 46.7 years.^{31,32} Mean values for gender (females) was 51.1% versus 66.7%, ($p > 0.13$) in agomelatine and the sertraline group, respectively who had MDD. In other studies, mean values for gender ranged from 51.4% to 70.6%.^{32,33}

Locality and marital status

Majority of patients in both the groups had rural residence, which is in concordance with national census 2011 which concludes that 90% of population in Himachal Pradesh

lives in villages.³⁴ An overwhelming majority of patients in both groups were married and almost 10% in both groups were widow. This was in contrast to the studies from the West, 34%-67% of the patients were either single, separated, divorced or widow which could be explained on cultural and ethnic differences.³⁵

Family type and educational status

Three quarters of patients lived in nuclear families in both groups, while other studies reported 53.4% to 81.3% patients living in nuclear families.³³ Loss of joint family system which provided healthy and supporting nurturing environment may be responsible for increasing prevalence of depression. Majority of patients in both groups were literate and graduates and the results were in comparison to previous studies.³⁶ Literate people with higher education tend to get depressed more due to unemployment, underemployment, peer pressure, workplace stress to perform and lack to work satisfaction.

Occupation

Majority of the patients in both groups were businessmen, followed by government employees and housewives. This was comparable to other studies and reasons could be increased competitive business environment.^{25,37} Government employees tend to have secure and stable job with stresses mostly limited to transfers and workplace stress.

Socio-economic class

Majority of patients belonged to the middle socioeconomic class (including upper middle and lower middle) as measured by modified Kuppuswamy's Socioeconomic Scale and only about 10% belonged to lower socioeconomic class in both the groups.³⁸ These were in comparison to other studies.³¹

Baseline Hamilton Depression Rating Score (HAM-D)

The mean values of HAM-D score at baseline between the two groups was statistically non-significant ($p > 0.28$). After 8-weeks, the mean values of HAM-D score between the two groups was again statistically non-significant ($p > 0.08$). However the difference was in favour of sertraline. This trend of possible favourable outcome in respect of sertraline was contrary to findings of previous studies which had shown that agomelatine was superior to sertraline in terms of efficacy and adverse effects in patients of MDD.^{31,33,39-41}

Clinical Global Impression Score for severity (CGI-S)

The mean values of CGI-S score at baseline between the two groups were statistically non-significant ($p > 0.10$). After 8-weeks, the mean values of CGI-S score between the two groups were again statistically non-significant ($p > 0.36$) but showed a trend towards better outcome.

Sertraline had decreased the CGI-S score to a greater extent with respect to agomelatine in various other studies.^{33,39,42,43}

Clinical Global Impression Score for improvement (CGI-I)

Mean values of CGI-I score at 2-weeks between the two groups were statistically non-significant ($p > 0.68$). After 8-weeks, the mean values of CGI-I score between the two groups were also statistically non-significant ($p > 0.12$), but showed a trend towards better improvement in sertraline group and this was in discordance with previous studies which showed that agomelatine was superior in comparison to sertraline to decrease CGI-I score more in patients suffering from MDD.^{31,33,41,44}

CONCLUSION

Both groups had shown significant decrease in scores of all scales i.e. HAM-D, CGI-S, and CGI-I at the end of 8th week as compared to baseline scores, indicating that the uses of agomelatine and sertraline have resulted in significant improvement in symptoms of patients of MDD and reinforcing their efficacy in treatment of MDD. Although no statistical difference was observed between two groups in the scores of HAM-D, CGI-S, and CGI-I after 8-weeks, however, favorable trend towards sertraline was seen though non-significant which was contrary to what was previously studied in terms of efficacy. Possible reasons could be differences in the cultural, lifestyle and ethnic variation between the Western world and our region as most previous studies were from the West.

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