**Vitamin D status in psychotic disorder patients and healthy controls – The influence of ethnic background**

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Abstract

Vitamin D deficiency is common among patients with psychotic disorders and could be due to unknown disease mechanisms or contingent factors. However most studies are performed in chronic patients and have often failed to address the influence of ethnicity on vitamin D levels in clinical samples. We investigated serum concentrations of 25- hydroxy vitamin D (S-25 OH D) in first episode patients compared to patients with multi episodes and healthy controls; with a specific focus on differences between visible ethnic minorities and participants from the majority population. A total of 284 participants were included in this cross-sectional study. First episode patients with a DSM-IV psychotic disorder were matched on age, gender and ethnicity to participants from a multi episode patient sample (1:1) and healthy controls (1:2). We did not find any differences between either patient groups or the healthy controls, but participants from visible ethnic minorities had significantly lower S- 25 OH D than participants from the majority population. This implies that S-25 OH D should be routinely measured in persons from visible ethnic minorities since low levels are associated with higher levels of depressive symptoms.

Key words: Early diagnosis, calcitriol, schizophrenia, ethnicity, seasons, case-control studies

## 1. Introduction

The active metabolite of vitamin D is a steroid hormone with multiple functions. It binds to the vitamin D receptor (VDR) which is found in most parts of the body, including the immune system (Fernandes de Abreu et al., 2009) and the central nervous system (Stumpf, 2012). Vitamin D is involved in the proliferation, differentiation and growth of neurons and has an important role in neuroplasticity (Deluca et al., 2013) both in the developing and adult brain.

Two recent meta-analyses have indicated significantly lower serum – 25 hydroxy vitamin D (S- 25 OH D) in patients with established psychiatric disorders compared to healthy controls (Belvederi Murri et al., 2013; Valipour et al., 2014), in line with previous studies showing an association between lower S-25 OH D and having a diagnosis in the schizophrenia spectrum (Rey-Sanchez et al., 2009; Partti et al., 2010). Correspondingly, in a study of diagnostically diverse psychiatric out-patients the lowest S- 25 OH D levels were found in patients with schizophrenia or autism spectrum disorders (Humble et al., 2010). There are thus relatively consistent indications of lower S- 25 OH D in patients with psychotic disorders, especially schizophrenia. To what extent the low vitamin D levels are related to (hitherto unknown) disease mechanisms or secondary to poor nutrition, reduced self-care or medication use is not known. Most studies have included chronic patients, i.e. groups that probably will be more influenced by these types of contingent factors than patients with a recent onset of their disease. However only two earlier studies have up to now been conducted in first episode/first treatment samples and their findings are equivocal. One study (N= 138) found significantly lower S- 25 OH D in both white and black patients, but not in patients of Asian origin, compared to healthy controls (Crews et al., 2013). The other small study (N= 40) did not find any patient/ control differences (Graham et al., 2014).

The main source of vitamin D is ultraviolet B (UVB) radiation from the sun. Dark skin (high pigmentation), , body-covering clothing and reduced outdoor activities, will interact with available UVB radiation, dependent on geographical latitude and season of the year, in affecting vitamin D

levels in the body (Wacker and Holick, 2013). This is of interest for the study of psychotic disorders since there are consistent findings of a higher incidence of psychotic disorders in immigrants and visible ethnic minorities, in particular dark-skinned immigrants to countries with predominantly white majority populations, i.e. countries at high latitudes (Cantor-Graae and Selten, 2005). There are however few studies of the associations between ethnic background and vitamin D levels in psychotic disorders. In the current clinical cross sectional study we thus aimed to explore differences in S- 25 OH D between a first episode psychosis patient sample, compared to a multi-episode patient sample and a healthy control sample matched for age, gender and ethnic background. We investigated if:

i) First episode patients and multi-episode patients have lower S- 25 OH D than the healthy controls

ii) Participants from visible ethnic minorities across the two patient groups and in the healthy control group have lower S- 25 OH D than participants from the majority population

## 2. Methods

Participants were recruited consecutively between May 2010 and April 2014 from in- and out-patient psychiatric units in the catchment areas of the four major hospitals in Oslo, as part of the larger Thematically Organized Psychosis (TOP) Study. The Regional Committee for Medical Research Ethics approved the study and our research methodology conformed to The Code of Ethics of the World Medical Association, Helsinki Declaration. All participants gave informed written consent to participate.

2.1. Participants

A power analysis based on group differences (means and standard deviations) from the previous vitamin D in FEP study (Crews et al., 2013) indicated that a group size of 46 participants would be sufficient to detect real differences given the expected differences and standard deviations. A total of 71 first episode patients (FEP) with a DSM-IV psychotic disorder (Schizophrenia spectrum i.e. schizophrenia, schizophreniform and schizoaffective, N= 46; other psychosis i.e. delusional disorder, brief psychotic episode, psychotic depressive disorder and psychosis NOS, N= 25) were included. Participants were defined as FEP if they gave consent to be recruited into the study within one year after start of their first adequate treatment (defined as admission to hospital or antipsychotic medication in adequate doses) for a psychotic episode (defined as at least one week with a score of four or more on Positive and Negative Syndrome Scale for Schizophrenia on items P1, P3, P5, P6 or G9). As a proxy for skin pigmentation the participants' ethnicity was used to divide the participants into two groups, one group (including participants with European ancestry (majority population group), and one group with participants of Asian, Latin -American and African ancestry (visible ethnic minority group). The FEP sample was then matched 1:1 on visible ethnic minority status, age, gender and diagnosis to a multi episode sample (MEP) and then matched 1:2 to healthy controls (HC) drawn from the same catchment area in the following manner: Participants from the majority population were directly matched with HC from the control group of the TOP study. Due to a low number with visible ethnic minority status in this control group, participants with visible ethnic minority background (i.e. from Asia including Turkey (N=17), Africa (N=17) and Latin-America (N=6)) were matched with HC of visible ethnic minority background (Asia including Turkey) from a population-based health study including immigrants to the city of Oslo; the Oslo Immigrant Health Study 2002 (http://www.fhi.no/artikler/?id=53584).

## 2.2. Procedures

### 2.2.1. Clinical

All patients were assessed by trained clinical research personnel. Demographic and clinical variables and the use of medication were obtained by clinical interviews by protocol and by conferring the medical records. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used for diagnostic purposes. In the FEP group, duration of untreated psychotic illness was measured in weeks. In the FEP and MEP groups total duration of illness (including treated and untreated phases) was measured in years and calculated as age minus age at onset. Current symptomatology was assessed by The Structured Interview for the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). At inclusion the participants went through a physical examination with blood sample withdrawal. Height and weight were measured by a standard procedure, and BMI was calculated by $kg/m^2$.

### 2.2.2. Biochemical

In the TOP sample; 25- OH D (25- OH D2 and 25- OH D3) serum concentrations were determined using a liquid chromatography- tandem mass spectrometry (LC-MS/MS) method developed at the Hormone laboratory (Oslo University Hospital, Norway) (supplementary materials 1). In the Oslo Immigrant Health Study, S- 25 OH D was measured by a radioimmunoassay (RIA kit from Diasorin) (Holvik et al., 2005). The equation LC/MS-MS = 1.16 x (RIA) -9 was calibrated at the laboratory for comparisons and the calibrated values from the Oslo Immigrant Health Study are used in the current study.

## 2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics v. 22 (IBM corp. 2014). The level of significance was preset to $p < 0.05$ (two tailed). Student t-tests and one way ANOVAs with Tukey post hoc tests were used for group comparisons of continuous variables, chi-square tests for categorical variables and Pearson's r for bivariate correlations. Normally distribution of the continuous variables

was evaluated by normality plots and found to be satisfactory with the exception of the assessments of duration of untreated psychosis and total duration of illness where we used Spearman's correlations. For statistical purposes, season was dichotomized into winter (December – May) and summer (June- November) (Porojnicu et al., 2007). For PANSS we used the five factor model by Wallwork (Wallwork et al., 2012). Seven participants had missing values for BMI; five had missing values for age at onset , three had missing values for in- vs out-patient status and nine had missing values for regular use of antipsychotic medication or not. In the multivariate analyses missing values were replaced with group means for independent continuous variables and mode (most used value) for independent dichotomous variables. To investigate the potential influence of confounders, variables that were either statistically significantly associated with S- 25 OH D or differed across groups (i.e. FEP, MEP or HC) or ethnicity (majority population or visible ethnic minority) in bivariate analyses were entered as covariates in an ANCOVA with S- 25 OH D as the dependent variable; here group membership (FEP, MEP or HC) and ethnicity were fixed factors in the model. The analyses were then repeated in the subsample containing only patients with a narrow schizophrenia spectrum diagnosis (schizophrenia n = 77, schizophreniform n = 8, schizoaffective n= 15). Finally we performed a second ANCOVA with group (FEP, MEP or HC) and season as fixed factors; gender, BMI and ethnicity as covariates to investigate the group by season interaction.

## 3. Results

The demographic and clinical sample characteristics are shown in table 1. Due to the matching procedure the age and gender by ethnicity distribution found in the FEP group were repeated in the MEP and in HC groups. The following variables differed between the groups: The MEP sample had significantly higher BMI than both FEP and HC with mean values slightly above upper limit of the normal range according to the WHO definition (range 18.5-24.9). The majority of HC had their blood samples taken during winter season. Concerning differences between the ethnic groups, there were

a larger proportion of males in the visible minority group than in the majority group (80% vs 60%, p= 0.001).

There were no significant differences in unadjusted S- 25 OH D between the FEP, MEP and HC. S- 25 OH D was lower in males, in samples drawn during the winter season and in visible ethnic minorities (table 2). Visible ethnic minorities had significantly higher BMI than participants from the majority population (mean 26.1 vs. 24.6 kg/m2, p= 0.003). There were no significant associations between age, BMI and S- 25 OH D in neither patient groups or in controls. In both patient groups (FEP and MEP) neither age at onset, tobacco consumption, regular use of psychopharmacological medication, being in- versus outpatient, duration of illness nor duration of untreated psychosis (in the FEP group) were associated with S-25 OH D (data not shown). S-25 OH D was not significantly correlated with the positive or the negative symptom factor from the PANSS (r = -0.07, p = 0.57 in FEP; r = -0.03, p = 0.81 in MEP and r = -0.15, p= 0.20 in FEP; r = 0.04, p = 0.74 in MEP, respectively). There was however a significant association between lower S-25 OH D and higher levels for the depressive symptom factor in FEP (r = -0.25, p = 0.04), but not in MEP (r = -0.07, p = 0.57). The first ANCOVA shows that the variation in S- 25 OH D was mainly explained by differences in ethnicity and seasonal variation (table 3). There was no effect of group membership (FEP, MEP or HC). The same results were found when the analyses were repeated, this time only including patients with a narrow schizophrenia spectrum diagnosis (data not shown). There was a trend level interaction effect (p= 0.06) between group (FEP, MEP or HC) and ethnicity; within the majority population there was lower S- 25 OH D levels in MEP than in HC while in visible ethnic minorities the pattern was the opposite way with higher S- 25 OH D in MEP than in HC . The differences did however not reach the preset level of statistical significance after controlling for BMI (table 3). The second ANCOVA shows that there was a group by season interaction effect (F= 4.02 (df 2,275), p= 0.02), based in higher variability across seasons in healthy controls: The highest S-25 OH D was found in healthy controls in summer season and the lowest in

winter season while S-25 OH D had more stable values across seasons in the patient groups (FEP and MEP).

In both FEP, MEP and in HC, S- 25 OH D was significantly lower in visible ethnic minorities than in the corresponding majority population (F= 11.85, p= 0.001 in FEP; F= 4.48, p = 0.04 in MEP and F=39.95, p< 0.001 in HC) (figure 1). There were no statistically significant differences in S-25 OH D levels between different ethnic minorities across groups. Participants of Latin- American ancestry however had nominally higher levels than participants with Asian or African ancestry (43.8 (29.5), p =0.5 versus Asia (31.8 (16.0)) and p= 0.6 versus Africa (32.5 (11.9)). Analyses within each clinical group showed that S- 25 OH D was nominally lower in MEP than in HC during summer season in participants from the majority population (46.8 $\pm$ 20.0 nmol/L vs. 60.3$\pm$ 17.2 nmol/L), but this difference did not reach the level of statistical significance (p = 0.06).

## 4. Discussion

In the current study we did not find any statistically significant differences in vitamin D status between a group of first episode patients, when compared to multi-episode patients and to healthy controls, respectively. There were however significant differences in S- 25 OH D between participants from visible ethnic minorities and participants from the majority population.

This first finding is in contrast to earlier case-control studies including patients with established psychotic disorders (Rey-Sanchez et al., 2009; Partti et al., 2010; Itzhaky et al., 2012; Jamilian et al., 2013). These previous studies however have methodological limitations, including lack of adjustment for ethnicity (Rey-Sanchez et al., 2009; Partti et al., 2010; Doknic et al., 2011; Jamilian et al., 2013), comparison between hospitalized patients and health care workers (Itzhaky et al., 2012) or hospitalized patients and healthy controls recruited by advertisements without control for place of residence (Crews et al., 2013). The healthy controls in the current study were randomly recruited from the same catchment area as the study patients and matched both for ethnicity and other

important confounding variables such as gender and age. A review of reported vitamin D levels from these previous studies actually show remarkably similar vitamin D levels for the patient groups, but with considerable variations in the levels of the control groups. Our analyses underline this as we found larger seasonal variations in vitamin D levels in healthy controls than in the patient groups.

The current findings are also in contrast to a previous study from our group, that found lower S-25 OH D in a clinical patient sample compared to a population based control sample, both from the Norwegian population (Berg et al., 2010). The main difference between the current study and the previous is that Berg used a control group where data on vitamin D, age and season for blood sampling were provided from a population study as means and standard deviations at group level. The current study has control samples with individual data for each participant, thus enabling us to match directly on important background variables including age. Since psychotic disorders have onset in adolescence or early adulthood, clinical samples can often be younger than the healthy controls, and this is of importance since there is a possibility for an age gradient in S-25 OH D levels. Since older and more chronic patient groups are more prone to be influenced by illness related lifestyle factors it is possible that investigations of this patient group will show differences between patients and controls independent of ethnic background.

Visible ethnic minority status was a strong predictor of low S- 25 OH D both in patients and in healthy controls. The crude observed difference in S- 25 OH D between ethnic groups could be inflated, because a large proportion of the HC group for administrative reasons had their S- 25 OH D measured during the winter season. However, ethnicity still had a strong and statistically significant effect on S- 25 OH D also after adjustment for season (table 3). These findings are in line with previous research in the area showing high levels of insufficient S- 25 OH D in visible ethnic minorities in Northern hemisphere (Holvik et al., 2005; Andersen et al., 2007). People living in Norway have poor access to vitamin D from the sun, because of high latitude and long winter seasons (Wacker and

Holick, 2013). In the absence of sun exposure through winter, diet and supplements become all the more important, but natural sources are few (mainly fatty fish and cod liver oil). Thus, cultural differences in diet can be one of the reasons for alarmingly low S- 25 OH D both in patients and healthy controls from visible ethnic minorities. Possibly, language barriers could also lead to a failure in reaching the ethnic minority population with advices regarding use of supplements. The finding that MEP from the visible ethnic minority group actually had higher S- 25 OH D during winter than summer could indicate that health care workers aware of their heightened risk of vitamin D deficiency during the winter season actively encouraged their use of dietary supplements. Our analyses also showed that the S- 25 OH D in healthy controls from the majority population varied more between winter and summer than in the corresponding patient groups. This could be explained by contingent factors such as reduced outdoor activities in the patient group during summer, compared to healthy controls.

This high proportion of patients with low S- 25 OH D is of importance since this might influence morbidity both related to depressive (Berg et al., 2010), positive (Yuksel et al., 2014), negative (Graham et al., 2014) or atypical symptoms (Dealberto, 2013). There were no significant correlations between S-25 OH D and positive or negative symptomatology in the current study, but there was a moderate association between low S-25 OH D and increased depressive symptomatology in the FEP group. Indications of an association between low S- 25 OH D and depression has been shown previously, but should be investigated further in a larger samples because vitamin D substitution could represent a possible intervention strategy in persons from visible ethnic minorities. We would however need randomized controlled trials to evaluate the effect. Another point of importance is that the risk of cardiovascular diseases and metabolic syndrome has been found to be associated with psychotic disorders (Johnsen et al., 2011; Ringen et al., 2014). Increased cardiovascular risk is also related to inadequate S- 25 OH D levels (Choi et al., 2014; Menezes et al., 2014; Ruwanpathirana

et al., 2014). Elevated risk of cardiovascular disease and metabolic syndrome in psychotic disorder in visible ethnic minorities has been demonstrated in long-term follow-ups (Henderson et al., 2005). It is thus of interest that, in our age and gender matched sample, visible ethnic minorities also had significantly higher BMI than the group recruited from the majority population, as well as lower S- 25 OH D.

While we did not find any differences in S-25 OH D between adult patients with psychotic disorders and healthy controls, prospective studies have suggested vitamin D deficiency as a contributing factor to higher risk of developing psychotic disorders in dark skinned immigrants (McGrath, 1999; Dealberto, 2007; Kinney et al., 2009; McGrath, 2011). There are also associations between vitamin D deficiency and known risk factors for psychotic disorders like urban living, winter births (Kendell and Adams, 2002) and migration (Dealberto, 2007). Since the main negative effect of vitamin D would be on brain development in earlier phases of life, our findings neither support nor contradict this hypothesis. However, the consistent findings of low S- 25 OH D in visible ethnic minorities do not contradict the need to explore the role of vitamin D deficiency as one possible contributor to the higher risk of psychosis in visible ethnic minorities.

An important strength of the current study is that the patient sample consists of both in- and out-patients, and thus can be seen as more representative of patients in general compared to samples recruited from inpatients' wards only. A major limitation to the study is the use of ethnicity as a proxy for skin pigmentation, even if we did not find significant differences in S -25 OH D between participants of Asian or African ancestry. We also lacked reliable information about the use of vitamin D supplements or time spent outdoors, factors that could influence S- 25 OH D in all participants. Another limitation is that two different methods for vitamin D measurements are used in the current study. They are however performed in the same laboratory, and the methods have

been cross-calibrated and the resulting equation has been used to calibrate the results to the same scale.

To conclude, participants from visible ethnic minority had significantly lower S- 25 OH D than corresponding patient- and control groups from the majority population and low S-25 OH D was associated with depressive symptoms in first episode patients. Vitamin D deficiency could thus be an important factor influencing symptom severity and co-morbidity in established psychotic disorder, in visible ethnic minorities already in early stages of illness. Clinicians should routinely measure S- 25 OH D in this patient group. However, our study did not support the findings of lower S- 25 OH D in young patients diagnosed with psychotic disorders, neither in first episode patients nor in multi episode patients, compared to healthy controls from the same geographical area. This finding was not influenced by adjustments for ethnicity, season for blood sampling, gender, age and BMI.

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Table 1. Demographic and clinical characteristics of the samples

| | **First episode** | **Multi episode** | **Healthy controls** | |
|---|---|---|---|---|
| | **FEP** | **MEP** | **HC** | |
| | **N= 71** | **N= 71** | **N= 142** | |
| | | | | |
| | **N (%)** | **N (%)** | **N (%)** | **Chi²** |
| Schizophrenia spectrum | 46 (64.8) | 54 (76.1) | | p = 0.14 |
| Male gender | 46 (64.8) | 46 (64.8) | 92 (64.8) | P = 1 |
| Ethnic minority status | 20 (28.2) | 20 (28.2) | 40 (28.2) | P = 1 |
| Summer season | 31 (43.7) | 38 (53.5) | 44 (31.0) | P = 0.01[a] |
| Medicated[b] | 59 (83.1) | 68 (95.8) | | P = 0.09 |
| AP/LIT/AE/AD/HYP[c] | 55/ 2/ 4/ 17/ 4 | 65/ 6/ 8/ 25/ 5 | | |
| Hospitalized | 31 (43.7) | 24 (35.3) | | p = 0.31 |
| | | | | |
| | **Mean (SD)** | **Mean (SD)** | | **ANOVA** |
| Age | 27.3 (8.2) | 28.0 (8.1) | 28.0 (7.6) | P = 0.80 |
| Age at onset | 24.5 (7.5) | 21.7 (7.0) | | P = 0.03 |
| BMI | 25.0 (4.0) | 26.8 (4.7) | 24.1 (4.0) | P < 0.01[d] |
| Positive symptoms[e] | 2.4 (1.0) | 2.2 (1.0) | | P = 0.30 |
| Negative symptoms[f] | 2.1 (0.9) | 2.0 (0.9) | | P = 0.47 |
| Depressive symptoms[g] | 2.4 (0.9) | 2.4 (1.1) | | P = 0.87 |
| Duration of illness[h] | 2.8 (4.1) | 6.3 (6.8) | | P < 0.01[i] |
| DUP[j] | 100.5 (22.6) | | | |

[a]Tukey post hoc test MEP > HC

[b]Regular use of psychopharmacological medication.

[c]Regular use of antipsychotics/ lithium/ anti epileptics/ anti-depressives/ hypnotics.
In FEP; 21 used a combination of psychopharmacological medication from more than one category, in MEP; 25

[d]Tukey post hoc test MEP > HC, FEP

[e]PANSS score (p1 + p3 + p5 + g9) / 4

[f]PANSS score (n1 + n2 + n3 + n4 + n6 + g7) / 6

[g]PANSS score (g2 + g3 + g6) / 3

[h]Duration of illness in years

[i]Non parametric Kruskal- Wallis test

[j]Duration of untreated psychosis in weeks

Table 2. Unadjusted serum concentrations of 25-OH vitamin D

| | **S-25 OH D nmol/L** | |
|---|---|---|
| | **mean (SD)** | |
| **First episode psychosis** | 44.8 (19.5) | |
| **Multi episode psychosis** | 43.1 (20.3) | |
| **Healthy controls** | 45.1 (21.4) | $F = 0.23^{df\ 2,281}$, p = 0.80 |
| | | |
| **Winter season** | 40.7 (20.4) | |
| **Summer season** | 50.3 (19.6) | $t = 3.96^{df\ 282}$, $p < 0.01$ |
| | | |
| **Ethnic minority status** | 29.5 (16.3) | |
| **Majority population** | 50.4 (19.1) | $t = 8.65^{df\ 282}$, $p < 0.01$ |
| | | |
| **Men** | 42.6 (19.8) | |
| **Women** | 48.1 (21.6) | $t = -2.16^{df\ 282}$, p = 0.03 |

Table 3. ANCOVA with S- 25 OH D as dependent variable, group (FEP, MEP, HC) and ethnicity as fixed factors

| | | | **95 % Confidence interval** | | **F (df)** | **significance** |
|---|---|---|---|---|---|---|
| | | **mean** [b] | lower bound | upper bound | | |
| **Gender** | | | | | 0.51 (1,275) | 0.48 |
| **BMI** | | | | | 0.01 (1,275) | 0.91 |
| **Season** | | | | | 6.63 (1,275) | 0.011 |
| **Ethnicity** | | | | | 47.20 (1,275) | <0.001 |
| **Group**[a] | | | | | 0.02 (2,275) | 0.98 |
| **Group*ethnicity** | | | | | 2.86 (2,275) | 0.06 |
| **Total sample** | | | | | | |
| | HC | 40.2 | 36.8 | 43.7 | | |
| | FEP | 40.6 | 35.9 | 45.3 | | |
| | MEP | 39.9 | 35.0 | 44.8 | | |
| **Majority population** | | | | | | **significance**[c] |
| | HC | 53.3 | 49.4 | 56.7 | FEP vs. HC | 1.00 |
| | FEP | 50.0 | 44.8 | 55.1 | FEP vs. MEP | 0.76 |
| | MEP | 45.7 | 40.4 | 50.9 | MEP vs. HC | 0.08 |
| **Visible ethnic minorities** | | | | | | |
| | HC | 25.4 | 19.4 | 31.4 | FEP vs. HC | 0.62 |
| | FEP | 31.8 | 24.4 | 39.2 | FEP vs. MEP | 1.00 |
| | MEP | 35.4 | 26.9 | 43.9 | MEP vs. HC | 0.27 |

[a]First episode psychosis (FEP), multi episode psychosis (MEP) or healthy controls (HC)

[b]S - 25 OH D nmol/L adjusted for gender, BMI and season

[c]Bonferroni adjustment for multiple comparisons

Figure 1.

S-25 OH D according to group (FEP, MEP and HC) and ethnicity, adjusted for gender, BMI and season