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Gluten consumption may contribute to worldwide obesity prevalence

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ABSTRACT: Gluten consumption has been controversially associated with obesity in previous studies. We sought to examine this association at the worldwide level.
Country specific data were obtained from 168 countries. Scatter plots, bivariate, partial correlation and multiple linear regression models were used to explore and compare the coincidence between obesity prevalence and consumption of gluten, non-gluten cereal protein and total cereal protein respectively. The established risk factors of obesity: caloric intake, sedentary lifestyle, urbanization, socioeconomic status, meat protein intake and sugar consumption were included in analyses as potential confounders. The 168 countries were also stratified into developing and developed country groupings for further examination of the relationships.
Worldwide, bivariate correlation analyses revealed that the strength and direction of correlations between all variables (independent, dependent and potential confounders) were at similar levels. Obesity prevalence was positively correlated to gluten consumption but was negatively correlated to consumption of non-gluten cereal protein, and was in almost nil correlation to total cereal protein consumption. These relationships were similar across all countries (n= 168), developed country grouping (N=44) and developing country grouping (n=124). When caloric intake, Gross Domestic Product at Purchasing Power Parity, sedentary lifestyle and urbanization were kept statistically constant in the partial correlation analysis, obesity was significantly correlated to gluten consumption in all countries, developed country grouping and developing country grouping, and was significantly but inversely and weakly correlated to non-gluten cereal protein in all countries and developing countries, and was in almost nil correlation to total cereal protein in all country groupings. Globally, stepwise multiple regression analysis, when all the independent variables and potential confounding factors were included, selected consumption of sugar as the variable having the greatest influence on obesity with $R^2 = 0.510$, while gluten was placed second increasing R^2 to 0.596.
Gluten consumption may have been emerging as an inconspicuous, but significant cause of obesity. While Westernization has driven the diet patterns worldwide to incorporate more gluten crops, obesity prevalence projection methods may estimate future obesity rates poorly if gluten consumption is not considered.

KEY WORDS: Gluten crops, ecological study, hidden association, obesity prevalence

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Abbreviations: WHO – World Health Organization; FAO – The Food and Agriculture Organization of the United Nations; UN – The United Nations; I_{bs} – Biological State Index; GDP PPP – Gross domestic product at Purchasing Power Parity; BMI – Body mass index; FODMAPs – Fermentable, Oligo-, Di-, Mono-saccharides And Polyols; SES – Socioeconomic Status

Background

Obesity is a medical condition, which is considered to contribute to chronic and noncommunicable disease load around the world (WHO 2015, Hruby and Fu 2015, WHO 2004). Obesity used to be considered as a health issue in the developed world, but now it is quickly emerging as a pandemic in the developing world. Despite various efforts made to reduce obesity prevalence, no national success has been achieved in the past two decades (Ng et al 2014).

Obesity is typically defined as excess body weight for height, but causes of obesity are complex and multifactorial. Traditionally, the combination of excessive energy intake, lack of physical activity and genetic susceptibility have been considered as causes of obesity (WHO 2015, Yazdi et al. 2015, Nguyen and El-Serag 2010). Recently, reduced natural selection has been postulated to contribute to obesity worldwide due to the accumulating obesity related genes/mutations in human populations (Budnik and Henneberg 2017; You and Henneberg 2018; Staub et al. 2018).

Over the last 20 years, the most prevalent dietary habit transitions were considered as the major contributor to obesity (Lau et al. 2006; Bojanowska and Ciosek 2016) because they may bring dietary risk factor exposure to susceptible people. However, the mechanism of how changed dietary factors cause obesity still remains complex and not well understood (You and Henneberg 2016a; Popkin et al. 2012). Dietary factors are influenced by economy and culture, this latter ones includes ideals of beauty besides eating habits and lifestyles..

Gluten ("sticky substance" in the Middle French) is a complex mixture of hundreds of related but distinct proteins, mainly gliadin and glutenin (Biesiekierski 2017; Freire et al. 2016; Wieser 2007). Gluten presents as the storage protein mostly in wheat (Biesiekierski 2017), and smaller amounts can be found in barley, oats and rye (Biesiekierski 2017; Blonstein and King 2012; Food and Drug Administration 2007) .In general, gluten makes up about 80% of total protein content in these four crops (Shewry 2007). Maize and rice also contain stored proteins, but they are different from gluten (Food and Drug Administration 2007).

Worldwide, gluten's particular properties such as water-absorption, cohesivity, viscosity, elasticity and chewy texture have been exploited in the bakery industry (Wieser 2007; Shewry et al. 2002; Lamacchia et al. 2014). However, in addition to established gluten-associated diseases such as celiac disease or wheat allergy, empirically, gluten diet has also been postulated as a risk factor for a number of further health issues, including obesity (Ludvigsson et al. 2013; Marcason 2011; Gaesser and Angadi 2012).

Wheat, the primary source of gluten, has been associated with obesity in a number of studies (Davis 2011; Hyman 2012; You and Henneberg 2016b). This association has been tested in the animal experiment where gluten free diets produced less weight gain (Soares et al.

2013), while gluten diet increased weight gain and adiposity (Freire et al. 2016). A gluten-free diet was recommended for weight management in different scientific and non-scientific sources (Hyman 2012; Gluten Free Therapeutics 2018; Petersen 2017).

There have been no published epidemiology studies revealing that gluten consumption is a risk factor for body weight increase. The reasons for lack of such studies may be:

1. Research participants come from the same cultural backgrounds with similar diet patterns (Davis 2011; Hyman 2012). Therefore, they consume similar levels of gluten crops which does not produce enough variance for revealing the association between gluten intake and body weight increase.
2. Maize and rice have been revealed to have the protecting role in body weight management (You and Henneberg 2016b), but generally they are consumed together with other cereal crops, including gluten rich cereals. This may lead to the cancellation of the body weight increasing effect of gluten crops by the other two staple food cereals, rice and maize (You and Henneberg 2016b; Ye et al. 2012).
3. The effect of gluten intake causes a delayed presentation (You and Henneberg 2016a, 2016b; Henneberg et al. 2011) .
4. Gluten-free food products mixed with high energy sugar or fats have been associated with body weight increase (Marcason 2011; Ye et al. 2012; Niewiński 2008; Crespo Escobar 2015), thus complicating understanding of gluten's role in causation of obesity by researchers and laymen.

While people are questioning if gluten consumption is a risk factor for obesity (Shewry 2009; Brouns et al. 2013), we considered the advantages of ecological study (Grant 2014; 2016) and conducted this ecological study to examine the association between gluten consumption and obesity prevalence in populations of the world based on empirical, macro-level data collected by international agencies across different populations, different cultural beliefs, and ethnicity related dietary patterns. We hypothesize that a measure of gluten consumption in a country, after correction for a number of factors known to influence obesity levels, will positively covary with obesity prevalence in a country

Materials and Methods

Data sources and selection:

International organizations, such as the WHO, FAO and the World Bank monitor and publish country specific data in relation to the health status, nutrition and diet, and economic development. These data have been helping governments, policy-makers, funders and researchers track and investigate the priorities of health research and development based on public health needs and ensure that funds and resources are used to meet the priorities. Their data have been recently used to examine the relationships between nutrients and obesity (You and Henneberg 2016a; 2016c; Soervo et al. 2014; Roccisano and Henneberg 2012) , diabetes (Basu et al. 2013; Basu et al. 2013; Weeratunga et al. 2014; You and Henneberg 2016d), and relationship between natural selection and obesity (Budnik and Henneberg 2017; You and Henneberg 2017) and type 1 diabetes (You and Henneberg 2016d), and cancers (Grant 2014, 2016; You and Henneberg

2017; You et al. 2018; You et al. 2018; Perrone and Grant 2015; You et al. 2018; You and Henneberg 2016e) respectively.

Data selection criteria followed in this study are:

– completeness of data across all analysed variables. Only countries with available data on both gluten consumption and obesity prevalence are included in this study. No country was excluded due to its population origins or cultural characteristics;
– in consideration of delayed presentation of effects of gluten consumption on obesity, the most recent available datasets were applied to reflect the current association between gluten intake and obesity prevalence.

The independent variables are the per capita gluten and non-gluten intakes which are defined as the total cereal protein consumption per person of a given country. They were captured and calculated with the food supply data (FAO 2015) on the proteins in cereal crops (wheat, barley, oats and rye) in grams per person per day in each country for the years 2011–2013.

These most up-to-date data on the per capita gluten and non-gluten intakes were captured from the Food Balance Sheet published by the FAO. The protein data consumption of the three years for each country were averaged to reduce the random error occurring when they were collected (You et al. 2019).

Considering about 80% of the protein in wheat, barley, oats and rye is gluten (Shewry 2009), the proteins sourced from these crops in the period 2011–2013 were summed and averaged to index the country specific level of per capita gluten consumption. We included all sources of gluten although the quantities from barley, oats and rye are very low due to limited consumption of these crops (Biesiekierski 2017; Maskova et al. 2011).

We subtracted the gluten protein of wheat, barley, oats and rye from the total cereal protein to create a variable "non-gluten cereal protein" for comparing different correlations between obesity and different combinations of proteins.

The United Nations Food and Agricultural Organization (FAO) food supply data collect total quantity of each food item at country level in consideration of production, imports, exports and changes in stocks (increases or decreases) (FAO 2001). The total quantity of food item is divided by the total population actually partaking in the total food supply during the reference period, which is 2011–2013 in this study (FAO 2001) to arrive at per capita consumption. Therefore, FAO data on food item may be objective and have an advantage over data collected through dietary surveys which have been criticized for the bias of underreporting (Subar et al. 2015).

The dependent variables in the analysis were the WHO Global Health Observatory (GHO) estimated data on the prevalence of adult obesity (percentage of BMI ≥ 30 kg/m^2 in country's population, 2014). The rationale for this decision is that three years is a practical period to develop obesity and metabolic syndrome after exposure to dietary risks (i.e., high intake of glutens today does not lead to immediate obesity) (Davis and Wansink 2015; den Engelsen et al. 2013; Trøseid et al. 2010). The most recent available gluten and non-gluten consumption data from the FAO are in 2013. Considering possible random errors in data reporting in single years, we averaged the gluten intake data between 2011 and 2013 to represent the intake during the three

years period. Accordingly, the WHO published 2014 obesity data were used in in this study because of delayed presentation of gluten effects) (Davis and Wansink 2015; den Engelsen et al. 2013; Trøseid et al. 2010).

The potential confounding variables are country specific data on: i) Total calories intake (kcal/capita/day), sugar and sweeteners (g/capita/day) and meat protein (g/capita/day). Data from 2011–2013 were extracted from the Food Balance Sheet of FAO, and then each variable was averaged over three years for data analysis. ii) GDP PPP, purchasing power parity in 2010 US dollars for comparability among countries as per the World Bank data bank (World Bank 2010). In order to explore the correlation between gluten consumption and obesity prevalence in countries with different socioeconomic status (SES), the 168 countries were grouped into the "developed" and "developing" worlds as per UN common practice designating countries based on economic level (United Nations Statistics Division 2016). iii) I_{bs} (Biological State Index), magnitude of obesity related gene/mutation accumulation in population (Budnik and Henneberg 2017; You and Henneberg 2016d, 2017) as per the supplemental files of the previous publication (Budnik and Henneberg 2017; You and Henneberg 2017). This magnitude may also reflect and include the population level rate of obesity developed in childhood due to metabolic faulty gene accumulation in human population (Budnik and Henneberg 2017). iv) Sedentary lifestyle, percent of population aged 18+ attaining less than 150 minutes of moderate-intensity physical activity per week, or less than 75 minutes of vigorous-intensity physical activity per week, or equivalent as defined in the Global Health Observatory conducted by the WHO (WHO 2015). and v) Urbanization, the percentage of the population living in urban areas as determined by the United Nations (UN) Population Division's World Urbanization Prospects (WHO 2010). We backdated these potential confounders for matching the same period of exposure to the gluten consumption with delayed obesity presentation in 2014 (You and Henneberg 2016c).

Globally, with income increasing and lifestyle Westernizing, the diet patterns, despite cultural differences, have been showing the signs of convergence towards a Western diet (Gopalan 1992; Pingali 2004; Noor 2002). For instance, rice had traditionally been the dominant staple food in Asia, but now the diet transition there is characterized by increased consumption of wheat (Pingali 2007), the primary gluten sourcing crop. The typical Western diet is featured with gluten sourcing cereals and food products containing gluten.

In order to explore the association between gluten consumption and obesity prevalence within individual countries from different areas, two countries from each WHO Region (WHO 2018) were randomly singled out and all their available population level gluten consumption data were obtained from the FAO Balance Sheet for the period of 1961–2013. The country specific gluten consumption data were aligned with their respective population level obesity prevalence data for association analysis.

Almost all the countries in the world have been driven towards Westernization, but at different pace due to different cultural and political backgrounds. To explore longitudinal associations between gluten consumption and obesity, we have extracted and aligned the year spe-

cific (1975–2013) raw data series on gluten consumption and obesity prevalence for performing scatterplots as well as to explore and visualize their longitudinal correlations in the selected countries in different WHO Regions. These countries are Kenya (African Region), Brazil (Region of the Americas), United Arab Emirates (Eastern Mediterranean Region), United Kingdom (European Region), Indonesia (South-East Asia Region) and Malaysia (Western Pacific Region) respectively. This analysis is able to show effects of different economic and cultural practices influencing food consumption and lifestyle in particular countries of different regions of the world.

Cereal crops are the primary source of gluten. Complementarily, the worldwide longitudinal association between population adjusted cereal consumption and population adjusted obesity prevalence was also explored. The independent and dependent variables are the worldwide cereals consumption data on annual basis, which were downloaded from the FAO website, and the obesity prevalence rate at global level, which was obtained through averaging the yearly WHO obesity prevalence rates for all the countries.

In this study, each country was treated as an individual subject. The country specific gluten consumption and obesity prevalence were aligned and a set of data consisting of 168 countries was obtained. Only the countries with the data on both gluten consumption and obesity prevalence were included in this study. The country specific data on cereal protein, non-gluten cereal protein, sugar & sweeteners, meat protein, calories, urbanization, GDP PPP, I_{bs} and sedentary life were aligned with the set of data for 168 countries. All the data were extracted and saved in Microsoft Excel® for analysis. The number of countries included in each analysis may have differed somewhat because not all the information was uniformly available for all countries due to various reasons. For example, they may not have supplied data to relevant UN agencies.

Data analysis

Our data analysis proceeded in four steps to examine the association between gluten consumption and obesity at population level:

1. Bivariate (Pearson's r and Spearman's rho) correlations were studied to evaluate the direction and strength of the correlations between all the variables across all countries.
   Nonparametric correlation was conducted to examine whether, globally, the Pearson's correlations between obesity prevalence and all variables differ due to potentially non-homoscedastic distribution of variables. Pearson's r was applied to analyse the longitudinal association between gluten consumption and obesity prevalence within the 12 individual countries selected from the six WHO regions. It was also applied to analyse the worldwide longitudinal association between cereals consumption and yearly averaged obesity prevalence rate.
2. Partial correlation of Pearson's moment-product approach was performed to identify the worldwide correlations between gluten consumption and obesity prevalence when the potential confounding variables, sugar & sweeteners, meat protein, urbanization, GDP PPP, calories, I_{bs} and sedentary lifestyle were kept statistically constant.

Pearson's r and partial correlation of Pearson's moment-product approaches were conducted respectively to explore the correlations between gluten consumption and obesity prevalence worldwide, in the developed world and the developing world respectively (United Nations Statistics Division 2016).

Gluten may be a risk factor independent of total calories intake. We explored this relationship in the 12 countries by correlating gluten intake standardised on total calories to obesity prevalence rate.

3. Standard multiple linear regression (Enter) was performed to summarize the descriptive statistics and to describe the correlations between obesity prevalence and the ten predicting and confounding variables, gluten, non-gluten cereal protein, cereal protein, sugar & sweeteners, meat protein, urbanization, GDP PPP, calories, I_{bs} and sedentary life. Standard multiple linear regression (Stepwise) was conducted to identify and rank the variables which had the greatest predicting effects on obesity prevalence.
4. Scatter plots were produced with the cross-country data (not transformed) in Microsoft Excel® to explore and visualize the strength, shape and direction of global association between gluten consumption and obesity prevalence.

   Scatterplots were also applied to explore and visualize the relationship between the global longitudinal cereals consumption and obesity prevalence. They were also applied to demonstrate the relationships between gluten consumption and obesity in the six representative countries, each of which is from different WHO Region.

Bivariate correlations, partial correlation and multiple linear regression analyses (Enter and Stepwise) were conducted with SPSS v. 24 on the log transformed variables. Fisher A-to-Z was calculated to assess significance of differences between pairs of correlation coefficients. The significance of association was kept at the 0.05 level, but 0.01 and 0.001 levels were also reported. Standard multiple linear regression analysis criteria were set at probability of F to enter ≤ 0.05 and probability of F to remove ≥ 0.10.

Results

Table 1 presents, worldwide, that, in Pearson's r analysis, obesity prevalence shows fairly strong correlation to gluten consumption ($r = 0.625$, $p<0.001$), nearly nil correlation to cereal protein, and significant, but negative correlation to non-gluten cereal protein ($r = -0.531$, $p<0.001$). Nonparametric correlations indicated similar relationships between gluten consumption ($r = 0.549$, $p<0.001$), cereal protein, and non-gluten cereal protein ($r = -0.515$, $p<0.001$) respectively (Table 1).

Pearson's r also revealed that GDP PPP was in significant correlation to both sugar & sweetener consumption ($r = 0.737$, $p<0.001$) and similarly strong to meat protein consumption ($r = 0.789$, $p<0.001$). GDP was also correlated to gluten consumption ($r = 0.625$, $p<0.001$), but the relationship was significantly weaker than correlation to sugar & sweetener ($z = -1.91$, $p<0.05$) consumption and meat protein consumption ($z = -3.05$, $p<0.01$) respectively (Table 1). In contrast, GDP PPP was in significant, but negative correlation to non-gluten cereal protein consumption. GDP

Table 1. Pearson's r (above the diagonal) and Spearman's rho (below the diagonal) correlation coefficients between all variables

Variable	Cereals protein	Cereals protein – gluten	Gluten	Sugar & sweeteners	Meat protein	Obesity	Urbanization	GDP PPP	Calories	I_{bs}	Sedentary lifestyle
Cereals protein	1	0.123	0.286***	−0.050	−0.153*	−0.006	0.036	0.003	0.248***	−0.010	−0.036
Non-gluten cereal protein	0.192*	1	−0.706***	−0.497***	−0.609***	−0.531***	−0.401***	−0.592***	−0.543***	−0.514***	−0.170
Gluten	0.384***	−0.760***	1	0.594***	0.541***	0.655**	0.463***	0.625***	0.617***	0.574***	0.366***
Sugar & sweeteners	−0.156*	−0.509***	0.439***	1	0.679***	0.715***	0.529***	0.737***	0.614***	0.665***	0.440***
Meat protein	−0.238**	−0.653***	0.487***	0.658***	1	0.680***	0.570***	0.789***	0.659***	0.648***	0.407***
Obesity	−0.039	−0.515***	0.549***	0.670***	0.614***	1	0.566***	0.598***	0.588***	0.565***	0.409***
Urbanization	−0.067	−0.466***	0.447***	0.568***	0.628***	0.625***	1	0.655***	0.591***	0.498***	0.381***
GDP PPP	−0.080	−0.622***	0.564***	0.690***	0.819***	0.582***	0.733***	1	0.758***	0.746***	0.489***
Calories	0.171*	−0.563***	0.645***	0.620***	0.685***	0.628***	0.644***	0.770***	1	0.620***	0.291***
I_{bs}	−0.130	−0.656***	0.549***	0.688***	0.777***	0.564***	0.665***	0.871***	0.757***	1	0.305**
Sedentary life	−0.079	−0.172	0.247**	0.387***	0.381***	0.401***	0.392***	0.446***	0.268**	0.287***	1

Significance level: *** $p<0.001$, **$p<0.01$ *$p<0.05$. Country number range: 130–168.
Data sources: Diet component and total calories variables from the FAO; Obesity prevalence rate and Sedentary life rate from the WHO; GDP PPP and urbanization from the World Bank. Ibs from previous publication (https://doi.org/10.1371/journal.pone.0170098).

PPP showed nearly nil correlation to cereal protein (Table 1). This may suggest that GDP PPP may not be a determining factor of level of cereal protein.

In partial correlation analysis (Table 2), obesity prevalence positively correlates to gluten consumption (r= 0.354, $p<0.001$), when sugar & sweeteners, meat protein, urbanization, GDP PPP, calories, I_{bs} & sedentary life were statistically kept constant.

Table 2 also shows that, in Pearson's r analysis, gluten consumption correlates to obesity prevalence in both developed (r = 0.465, $p<0.001$) and developing (r = 0.611, $p<0.001$) country groupings. Contrarily, non-gluten cereal protein consumption negatively correlates to obesity prevalence in both developed (r = −0.299, $p<0.05$) and developing (r = −0.480, $p<0.001$) country groupings. Again, cereal protein consumption did not show any correlation to obesity prevalence in either of the two country groupings.

Although correlations (Pearson's r and partial) between obesity and gluten consumption seem stronger in developing country grouping than those in the developed country grouping, the difference does not reach the significance level in Fisher A-to-Z analysis.

Worldwide, in the partial correlation analysis, gluten intake explained 12.53% of obesity statistically independent of the seven risk factors, Sugar & sweeteners, Meat protein, Calories, GDP PPP, I_{bs}, Sedentary life and Urbanization (Table 2).

In multiple regression analysis (Table 3) gluten consumption is one of the significant predictors (β = 0.397, $p<0.001$), second only to sugar & sweeteners (β = 0.357, $p<0.001$), of obesity prevalence in the Enter procedure in which all the variables (sugar & sweet-

Table 2. Pearson r and partial correlations of gluten consumption to obesity prevalence in all countries, and in developed and developing country groupings

Variables	All countries				Developed Country Grouping				Developing Country Grouping			
	Pearson's r		Partial		Pearson's r		Partial		Pearson's r		Partial	
	r	n	r	n	r	n	r	n	r	n	r	n
Gluten	0.655***	168	0.354***	121	0.465***	44	0.366*	29	0.611***	124	0.349***	83
Cereals protein	−0.006	168	0.052	121	0.097	44	0.153	29	−0.014	124	0.004	83
Non-gluten cereal protein	−0.531***	168	−0.191*	121	−0.299*	44	−0.157	29	−0.480***	124	−0.285**	83
Sugar & sweeteners	0.715***	168	–	–	0.389**	44	–	–	0.692***	124	–	–
Meat protein	0.680***	168	–	–	0.386**	44	–	–	0.645***	124	–	–
Calories	0.588***	168	–	–	0.380*	44	–	–	0.531***	124	–	–
GDP PPP	0.598***	166	–	–	0.024	44	–	–	0.574***	124	–	–
I_{bs}	0.565***	168	–	–	0.021	44	–	–	0.466***	124	–	–
Sedentary lifestyle	0.409***	130	–	–	−0.025	38	–	–	0.487***	92	–	–
Urbanization	0.566***	168	–	–	0.038	44	–	–	0.502***	124	–	–

Significance level: *** p<0.001, **p<0.01 *p<0.05.

Data sources: Diet component and total calories variables from the FAO; Obesity prevalence rate and Sedentary life rate from the WHO; GDP PPP and urbanization from the World Bank. I_{bs} from previous publication (https://doi.org/10.1371/journal.pone.0170098).

eners, gluten, meat protein, GDP PPP, urbanization, cereal protein, non-gluten cereal protein, calories, I_{bs} and sedentary lifestyle) were entered and examined simultaneously. When the same predictor variables were entered, the stepwise linear regression analysis selected gluten consumption as the independent variable to have the second greatest influence (adjusted $R^2 = 0.596$) on obesity prevalence behind sugar consumption. Neither cereal protein nor non-gluten cereal protein were chosen as strong or significant predictor in the Enter regression analysis or selected as the variable in Stepwise regression. The stepwise

Table 3. Linear regression analyses (Enter and Stepwise) to predict obesity prevalence

All variables entered	Enter Model		Stepwise Model	
	β	Sig.	Rank	Adjusted R^2
Sugar & sweeteners	0.357	<0.001	1	0.510
Gluten	0.397	<0.001	2	0.596
Meat protein	0.366	<0.001	3	0.645
GDP PPP	−0.405	<0.001	4	0.668
Urbanization	0.124	0.076	5	0.678
Cereals protein	−0.091	0.180	Insignificant predictor	–
Non-gluten cereal protein	−0.047	0.611	Insignificant predictor	–
Calories	0.111	0.229	Insignificant predictor	–
I_{bs}	−0.081	0.332	Insignificant predictor	–
Sedentary lifestyle	0.089	0.156	Insignificant predictor	–

Data sources: Diet component and total calories variables from the FAO; Obesity prevalence rate and Sedentary life rate from the WHO; GDP PPP and urbanization from the World Bank. I_{bs} from previous publication (https://doi.org/10.1371/journal.pone.0170098).

Table 4. Associations (longitudinal, across years 1975–2013) between gluten consumption and obesity prevalence within twelve representative countries

WHO Region	Country	r			r		
		Pearson's	*p*	n	Gluten/calories	*p*	n
Africa	Kenya	0.848	<0.001	39	0.8933	<0.001	39
	Tanzania	0.691	<0.001	39	0.8774	<0.001	39
Americas	Brazil	0.597	<0.001	39	0.4002	<0.01	39
	United States	0.801	<0.001	39	0.7899	<0.001	26*
Eastern Mediterranean	United Arab Emirates	0.461	<0.01	39	0.5043	<0.001	39
	Yemen	0.725	<0.001	39	0.8762	<0.001	39
Europe	United Kingdom	0.930	<0.001	39	0.9180	<0.001	39
	Germany	0.675	<0.001	39	0.9787	<0.001	39
South-East Asia	Indonesia	0.951	<0.001	39	0.9467	<0.001	39
	Thailand	0.931	<0.001	39	0.9328	<0.001	39
Western Pacific	China	0.266	0.102	39	0.9610	<0.001	16*
	Malaysia	0.887	<0.001	39	0.8733	<0.001	39

Significance level: *** p<0.001, **p<0.01 *p<0.05.
Data sources: Gluten consumption data from the FAO; Obesity prevalence rate from the WHO.
*United States and China took the gluten consumption data from the periods of 1975 to1990 and 1975 to 2000 respectively.

regression indicates that, statistically, gluten consumption explains about 8.60% increase in worldwide obesity prevalence.

Table 4 shows that gluten consumption correlates to obesity prevalence at different strength and significance levels in all the twelve countries from the six WHO Regions. However, the correlation in China is weak (r = 0.266, p = 0.102).

In general, gluten intake standardised on total calories correlated to obesity prevalence rate significantly. This suggests that gluten consumption may be another contributor to obesity prevalence independent of total energy intake and economic and cultural circumstances of a particular country (Table 4).

Figure 1 shows the worldwide association between gluten consumption and obesity prevalence. It is best described by the power curve with moderately strong correlation (r = 0.655, p<0.001, Figure 1-1). The weaker relationship is revealed between cereal consumption and obesity prevalence (r = 0.388, p<0.01) (Figure 1-2).

Figure 2 shows that, longitudinally from 1975, gluten consumption correlates to obesity prevalence in Kenya (r = 0.879, p<0.001, Figure 2-1), Brazil (r = 0.651, p<0.001) (Figure

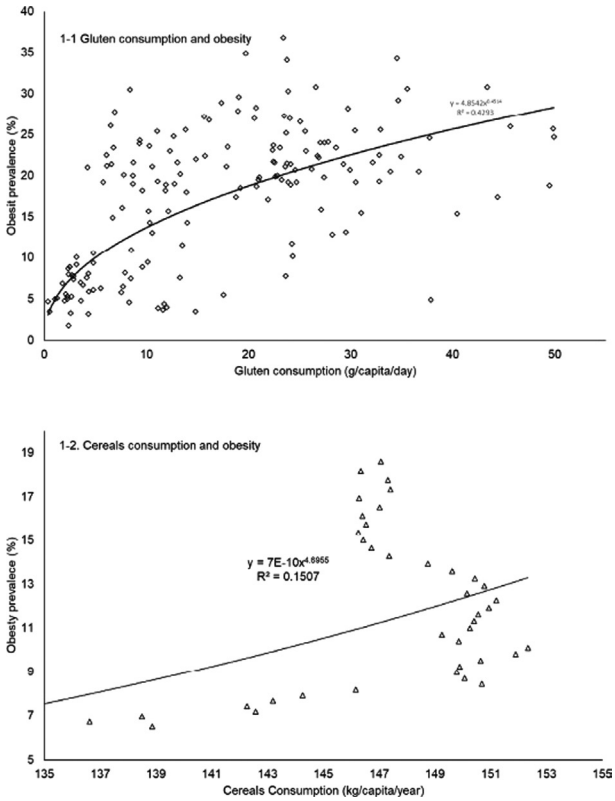

Fig. 1. Worldwide associations between obesity prevalence and gluten consumption and cereals consumption respectively

Data sources: Gluten consumption data from the FAO; Obesity prevalence rate from the WHO.

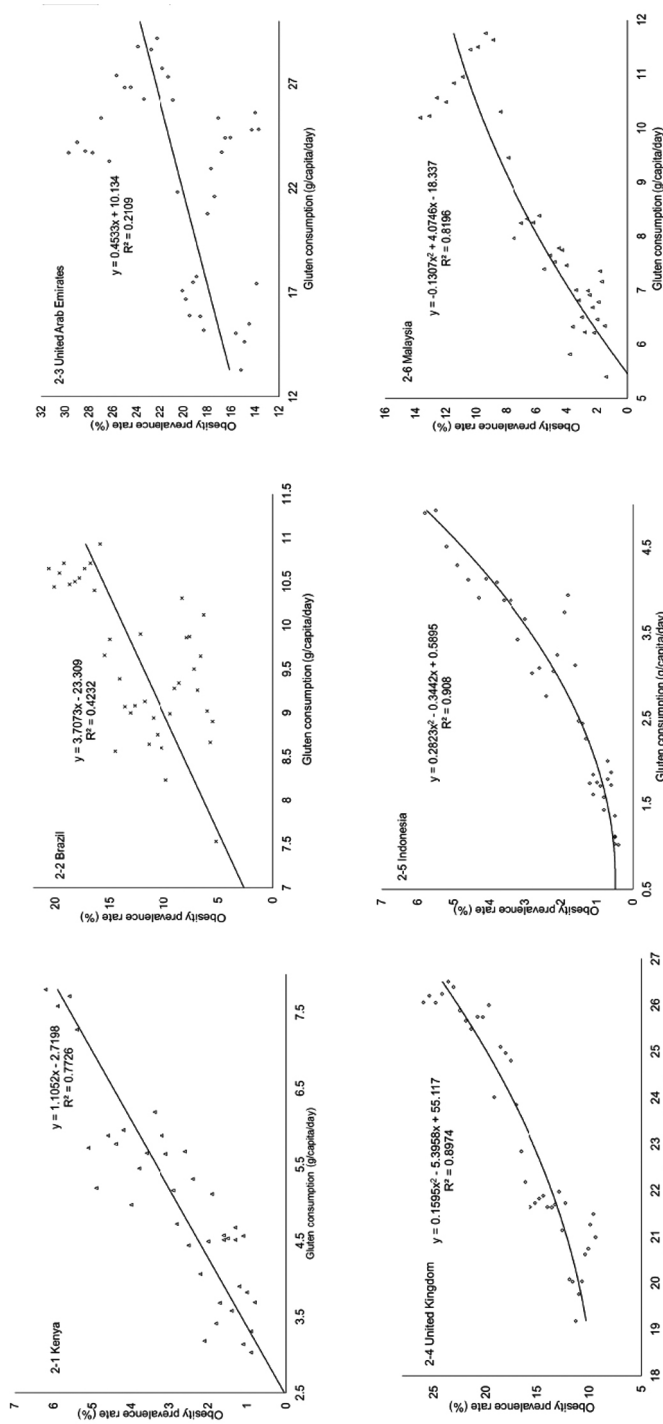

Fig. 2. Country-specific correlation of gluten consumption and obesity in 30 consecutive years (1975–2013)
Data sources: Gluten consumption data from the FAO; Obesity prevalence rate from the WHO.

2-2), United Arab Emirates (r = 0.459, $p<0.01$) (Figure 2-3), United Kingdom (r = 0.942, $p<0.001$, Figure 2-4), Indonesia (r = 0.953, $p<0.001$) (Figure 2-5) and Malaysia (r = 0.905, $p<0.001$) (Figure 2-6).

Discussion

This ecological study examined the relationship between gluten consumption and obesity prevalence at country level. Despite the multifactorial causation of obesity, our statistical analysis results indicated that countries with the greater gluten consumption had the higher obesity prevalence rate. Statistically, gluten consumption is a significant predictor of obesity, and this relationship is independent of the effects of sugar & sweeteners, meat protein, urbanization, GDP PPP, calories, I_{bs} and sedentary lifestyle that all also have significant effects on obesity prevalence.

Globally, more and more gluten consumption has been seen in our daily diet due to the growing Westernization of diet (Tovoli et al. 2015), which may have driven the increase of gluten crops share in wheat-based Mediterranean diet (Volta et al. 2013; Guandalini and Polanco 2015) and the replacement of rice, the dominant component in the diets in Asia, the Middle East, and North Africa (Tovoli et al. 2015). Reduction of dough fermentation time by the bakery industry has even encouraged the breeding of crops with higher gluten content.

There are several underlying (patho-) physiological mechanisms offering possible explanations for the identified statistical relationship between gluten consumption and obesity prevalence, which we would like to discuss below.

Gluten triggers immune-related inflammation and insulin resistance, which may increase human body weight (Soares 2013; Jamnik et al. 2015), while some gluten peptides have even been shown to be cytotoxic (Volta et al. 2013; Belderok 2000). This postulation was supported by the studies of animal model (Soares 2013) and human subjects with celiac disease (Lebwohl et al. 2015) and without celiac disease (Jamnik et al. 2015). Soares et al. (2013) fed mice with a high-fat diet containing 4.5% gluten (control) and a diet without gluten for 8 weeks. Mice on gluten free diet presented a reduction in body weight gain and adiposity. With the cross-sectional examination of 1,095 adults, Jamnik et al. (2015) concluded that gluten consumption is associated with increased plasma-2-macroglobulin (a marker of inflammation) in adults without celiac disease. A number of studies reported that anti-nutrients contained in gluten proteins may cause inflammation (Davis 2011; Hyman 2012; de Punder and Pruimboom 2013) which, accordingly, may increase body weight of mammals (Soares et al. 2013) and humans (Davis 2011; Hyman 2012; Cheng et al. 2010).

Leptin is an important hormone produced by white adipose tissue to regulate energy expenditure in human body (Jönsson et al. 2015). Leptin resistance has been hypothesized as one of the major obesity risks, and it has been associated with gluten diet. People with obesity tend to have high level of leptin in their circulation, which makes them more susceptible to develop leptin resistance if they are on gluten diet (Jönsson et al. 2005, 2015). The correlation between gluten consumption and body weight increase has been successfully tested in an animal model of obesity with the re-

sult that gluten may reduce thermogenesis and energy expenditure in mammals (Freire et al. 2016).

It was reported that, in modern diet, fats and carbohydrates may provide enough calories to meet our minimum dietary energy requirements (You and Henneberg 2016a, 2016c). Because meat protein may be digested later than carbohydrates and fats (You and Henneberg 2016a, 2016b; Henneberg et al. 2011) the energy from meat protein may become the surplus which is saved and stored as fat in human body and thus, contributes to obesity directly (You and Henneberg 2016a, 2016b; Henneberg et al. 2011). Gluten is a composite plant protein and it may be metabolized later than carbohydrates and fats, which is similar to animal proteins (You and Henneberg 2016a, 2016c; Grantham et al. 2018). This may make energy from gluten become the surplus energy as well, and contribute to obesity (You and Henneberg 2016a, 2016c; Grantham et al. 2018). Low fat foods leading to less weight gain has been advocated as the healthy food guideline in terms of body weight management. This may not conflict with our study. The reason may be that the energy from gluten (protein) may be used, at least part of, to meet human daily need if fat, as the energy dense food component, is consumed less leading to less available energy in human body.

Gluten providing energy surplus, triggering immune-related inflammation and metabolic syndrome (insulin and leptin resistance) may explain the mechanism for gluten to increase body weight leading to obesity. Therefore, the contributing effect of gluten to body weight increase may be a slow process, and obesity may be the delayed presentation of gluten consumption. This is supported by a recent study which reported that a group of healthy "Caucasian Danish adults" started to lose body weight (on average 0.8 ± 0.3 kg) after eight (8) weeks on the low-gluten diet (Hansen et al. 2018).

In summary, it may no longer be acceptable that, like macronutrients, such as fats and carbohydrates, gluten is just a source of calories in our daily diet. The findings of this study suggest that gluten may contribute to body weight increase through altering human metabolism and providing energy surplus.

Zong et al. (2018) conducted a cohort study on the relationship between gluten consumption and type 2 diabetes. Three cohorts were included in Zong et al.'s study (2018) the Nurses' Health Study (NHS female nurses, 30–55 years old), the NHS II (female nurses, 20–44 years old) and the Health Professionals Follow-Up Study (HPFS, male health professionals, 40–75 years old). There are several flaws in this study:

1. All three study cohorts were health professionals, who were well educated and had very strong health care knowledge and skills. Education level is inversely correlated to body weight increase. In this study, none of the three cohorts was observed to have higher BMIs, and none of the cohort had the BMI over 30.
2. The correlation identified in this study may be flawed in the two female cohorts as the research subjects were in the reproductive or menopause periods. The obvious reason may be that female animals are generally excluded from investigating how diet/nutrition affects the body weight changes primarily due to estrogen fluctuation.
3. The confounding factors, such as total calories intake and sedentary life-

style were not included for the data analysis.

Therefore, the relationship between gluten consumption and BMI reported in this study may not contradict our hypothesis that gluten consumption is associated with obesity. Our study included entire adult populations (both sexes, aged 18+) and controlled for seven (7) major obesity risk factors in statistical analysis.

Interestingly, our statistical analysis showed that different cereal protein combinations (gluten, non-gluten cereal protein and total cereal protein) have contrasting effects on obesity. Gluten was significantly associated with obesity, but non-gluten cereal protein showed the negative and significant correlation with obesity in general. Total cereal protein showed almost nil correlation to obesity. These correlations may suggest that the adverse effects of gluten to increase body weight, and beneficial effects of non-gluten cereal proteins to reduce obesity may be balanced in the intriguing ways.

Longitudinal association between gluten consumption and obesity prevalence was identified in different countries from all the six WHO regions in this study. Comparing to the other 11 countries, the association in China is much weaker in bivariate correlation. This weak association in China may be confounded by incomplete Westernization process, and/or intermittent anti-Westernization campaigns, which may make the level of Western diet featuring gluten consumption to fluctuate. An alternative explanation may be the drastic economic development in the past decades that has driven Chinese to eat more meat products.

To the best of our knowledge, there have been no epidemiology studies identifying correlation between gluten consumption and obesity. There may be several reasons:

1. Due to easy affordability of gluten crops as the staple food component, research participants may have the same level of gluten crop intake which does not produce enough variance for identifying the association between gluten intake and body weight increase.

   Our data analysis showed that GDP PPP was correlated to gluten consumption significantly weaker than to meat consumption, and sugar and sweetener consumption. This suggest that gluten sourcing crops (wheat barley, oats, and rye), which are staple food crops, are easily affordable to almost all people due to advanced plant breeding techniques, low cost of transportation, storage and circulation (You and Henneberg 2016b). Therefore, people at different SES levels may not have the significant difference in the quantities of intake of gluten crops if they are on the similar diet patterns. In other words, it is the diet pattern, instead of affordability (GDP PPP), that influences the level of gluten crop consumption. It may indicate that populations which are more westernized tend to consume more gluten, but less non-gluten cereal protein. Similar to the finding in this study, You and Henneberg (2016b) reported that, due to homogeneities of diet patterns and SES among European populations, wheat, the primary source of gluten, was not in significant correlation to obesity prevalence in European region while it correlated well in other regions.

   Numerous individual testimonials in different populations or ethnicities in-

dicated that gluten may increase body weight for people on gluten diet, but no statistical correlation has been reported. Probably, people who made such testimonials are from the same or similar diet patterns and cultural backgrounds (Davis 2011; Hyman 2012), which did not allow the researchers to identify the correlation between gluten consumption and obesity because of small variance of gluten consumption among these people. In our study, the two country specific variables (gluten consumption and obesity prevalence) were collected across countries, cultural beliefs, including religions, and ethnicities. These cross-sectional data mean that our research data are subject to different diet patterns, which determine, statistically, significantly different levels of gluten consumption.

2. The effect of gluten (crop) intake on increasing body weight is balanced when, practically, it is consumed together with non-gluten crops which have the opposite effect on reducing body weight, such as maize and rice (You and Henneberg 2016b).

   Total cereals, instead of individual cereal crops, have been advocated as the healthy food group in terms of body weight management (Ye et al. 2012). This protective role of total cereal consumption on maintaining health can be traced back to the Renaissance period (1400's) (Gaeta et al. 2013). The Renaissance elite with upper social status on animal rich diet had higher risk of developing atherosclerosis than those with lower social status who primarily lived on cereal-based diet (Gaeta et al. 2013).

   Our study indicated that gluten might have adverse effect on body weight management, but this adverse effect may be balanced by the non-gluten cereal protein. These balanced effects of gluten and non-gluten cereal protein on body weight management make total cereal protein consumption not to correlate with obesity, which is consistent with the constant advocacy about the beneficial effects of total cereals on body weight management. Accordingly, these balanced effects can allow gluten to contribute to obesity without being easily noticed.

3. The effect of gluten intake on body weight increase may be a delayed presentation, and the slowly accumulated effect may only become noticeable after high gluten intake for years.

   Overeating and sedentary lifestyle have been considered as the obesity risks (Brouns et al. 2013). Their impacts are direct, sizeable and immediate. However, gluten consumption can contribute to obesity differently and slowly. It has been reported that gluten consumption may increase human body weight through increasing inflammation and insulin resistance (Davis 2011; Hyman 2012; Soares et al. 2013; Jamnik et al. 2015; Lebwohl et al. 2015; de Punder and Pruimboom 2013), reducing energy expenditure (Freire et al. 2016), and providing caloric surplus in human body (You and Henneberg 2016a, 2016b; Henneberg et al. 2011). The correlation between gluten and obesity in our study was independent of the simple energy intake (total calories) and expenditure (sedentary lifestyle). This suggests that the mechanism for gluten as a kind of protein to contribute to body weight increase cannot be explained with simple concept of energy in and energy out.

4. Obesity researchers and laymen have been potentially confused with the correlation between gluten-free food products and body weight increase because high energy food component has been added into gluten-free food products.

   Although there is no experimental evidence or clinical trial to show that the established correlation between gluten consumption and chronic diseases, such as celiac disease or wheat allergy, gluten diet has also been postulated as a risk factor for a number of further health issues, including obesity (Marcason 2011; Davis 2011; Hyman 2012). Professionals in obesity research and lay people may be confused by some studies reporting that gluten-free diet can increase human body weight as well (Ye et al. 2012; Niewinski 2008). This confusion was clarified by a recent study which found that gluten free diet contains more added high energy macro-nutrients, fatty acids and lipids, than gluten containing food products which may lead to obesity (Marcason 2011; Crespo Escobar et al. 2015).

   The association between cereals consumption and obesity has been identified in this study, and the relationship was noted to be exponential ($r=0.388$) This relationship is in agreement with the association between gluten consumption and obesity. The underlying reason may be that cereals are the primary source of gluten. Additionally, cereals are rich in carbohydrates which increase blood acidity level (Liao et al. 2018). This process may burden cardiorespiratory system and alter aldosterone balance (Liao et al. 2018) to cause hyper insulinemia and promote abdominal fat deposits (Liao et al. 2018). Alternatively, cereals intake contributes to obesity because they contain large amount of carbohydrates which may cause insulin resistance, and thus obesity (McKeown et al. 2004).

There are several intrinsic limitations in this study:

1. Firstly, the ecological analysis approach adopted in this study has the intrinsic limitation which is conceptualized as the ecological fallacy (You and Henneberg 2016a; Morgenstern 1995). It is neither ethical nor logically feasible to consider whole countries to represent uniformly different socioeconomic levels, urbanization, caloric intake or any food crop consumption. However, we tried to control for as many available variables as possible in this study to reduce their potential influence on the correlation between gluten consumption and obesity prevalence.
2. Secondly, some variables may influence the identified correlation in this study, but, statistically, their influences are nearly impossible to remove. For example, carbohydrate consumption could contribute to body weight increase indirectly as carbohydrates may be digested earlier than gluten (You and Henneberg 2016a). Fermentable carbohydrates, referred to as FODMAPs (Fermentable, Oligo-, Di-, Mono-saccharides And Polyols), although their quantity is small, could play a role in developing obesity (Biesiekierski and Iven 2015; Muir and Gibson 2013). Moreover, comparing to the conventional diet, gluten free diet may lose the protective role of non-gluten cereal protein and micronutrients on body weight management (Via 2012). However, due to

lack of the availability of such data, the potential confounding effects of these food components could not be controlled for in our data analysis.
3. Thirdly, the food variables included in our study are, theoretically, the supply of each diet component in each country, rather than their direct consumption, which may not consider food wastage (Siervo et al. 2014).
4. Fourthly, staple food, such as gluten crops, of a population in a particular region is not really a choice of people. It depends on ecological and economic variables including climate and water availability for agricultural production. However, we cannot remove the potential confounding effects of these diet patterns determining factors on our analysis results.
5. Finally, the correlation between gluten consumption and obesity prevalence was identified at country level. Therefore, it does not necessarily hold true at individual level (You and Henneberg 2016c; Morgenstern 1995). However, the constant and significant correlation between gluten consumption and obesity revealed in this study is worth further exploration within the cohorts in which the quantities of gluten consumption by individuals can be differentiated.

Conclusions

Gluten contributes to obesity prevalence worldwide, but this adverse effect is not easily noticeable as the intake of other nutrients, such as non-gluten cereal proteins obscures it in some analyses indicating that whole cereal consumption shows the protective role in maintaining human body weight. Since, globally, the diet pattern has been Westernized to incorporate more gluten, obesity prevalence projection methods should consider the effects of gluten consumption on body weight increase in the future.

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The Authors' contribution

WY and MH conceived the study and conducted the data analyses. WY, FR, PE, FG, PD and MH interpreted the data. WY drafted the manuscript with the input of FR, PE, FG, PD and MH. All authors reviewed, edited and approved the final manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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