Health Benefits of Wholegrain - A Systematic Review of the Evidence to propose a daily intake recommendation

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Background and Objectives:

Recommendations to include **wholegrain (WG)** in the daily diet are widespread but they are rarely quantitative. The objective was to **systematically review the published human studies** aiming at identifying the **daily intake of WG associated to favorable health outcomes** including cardiovascular disease (CVD) and type 2 diabetes risks (T2D).

Methods:

PubMed and Cochrane Library were searched from 01/01/1993 to 12/31/2012 for CVD and from 01/01/1993 to 12/31/2014 for T2D. Because of the global objective of this work, key words related to several health outcomes (overall mortality, obesity, cardiovascular diseases, T2D and associated risk factors) were used. Observational and intervention studies were considered. Study selection and data extraction were performed by two PhD and one nutritionist (**figure 1**). WG intakes were standardized in g/d of **WG ingredients (WGI)** by using the following assumption[1]:

- 1 serving of WG food = 30g
- WG foods contain on average 51% of WGI

For CVD, a meta-analysis by multivariate-adjusted risk ratios (HR, RR or OR) of CVD was done comparing the highest and lowest percentiles of WG intake. Another meta-analysis (MA) was performed in order to **explore the quantitative relationship between WGI intake and the risk of** CVD and T2D . Meta-regressions of coronary endpoints and T2D rates on WGI amounts were performed by using a hierarchical mixed linear model, with exploration of covariates [sex, age, country, study design, mode of report of WG intake (food or ingredient), duration of follow up]. All statistical analyses were performed on SAS 9.2. Missing information was requested from the authors when needed. If no appropriate answer was received and if the missing information could not be calculated from the publication, the study was excluded from the MA.

Subset of key words used in the literature search.

WG-related keywords	T2D-related keywords	CVD-related keywords
WG OR bran OR individual cereal name (wheat / rye / braley / oat…) NOR (germ/aleurone)	e.g. Diabetes / insulin sensitivity / hyperglycemia / glucose tolerance …	e.g. cardiovascular OR cardiometabolic OR blood cholesterol OR LDL cholesterol OR triglyceride OR blood lipids OR blood pressure OR infarct OR heart failure OR stroke OR cerebrovascular accident OR ischemic heart disease OR coronary heart disease …

Results and Discussion:

- **8 studies were identified for T2D and 6 studies for CVD.**
- WG intake ranged from 2 to 154 g/day (median is 20 g/day) in the studies dealing with T2D risk.
- The meta-analysis by multivariate-adjusted risk ratios of CVD displayed a significant association between WGI intake and the risk of CVD; this confirm previously published meta-analyses.
- The overall **Relative Risk estimate was 0,84** with the random effect model (p=0.004).
- The meta-regression analysis failed to demonstrate a significant relationship between WGI intake and the rate of coronary events (p=0.67) : This may be due to a great heterogeneity between studies, to the high influence that each individual study (with its particular characteristics regarding the WG intake level, sex, event rate…) exerts on the results, and a to lack of power (only 4 studies)
- **Significant association between WGI consumption and occurrence of T2D (p<0.0001)**, with a slope of -0.000293 (95% CI: [-0.000424, -0.000161]), i.e. an overall **reduction of 0.3% in the incidence of T2D for each additional 10 g of WGI consumed daily** (**figure 2**).
- Secondary analyses showed that the results are robust with regard to either exclusion of each study at a time or accounting for all tested covariates. Observed results did not show evidence of between-study heterogeneity (Cochran Q statistic ; Q = 0.11, p=0.99).

Figure 1: Flow diagram of study selection

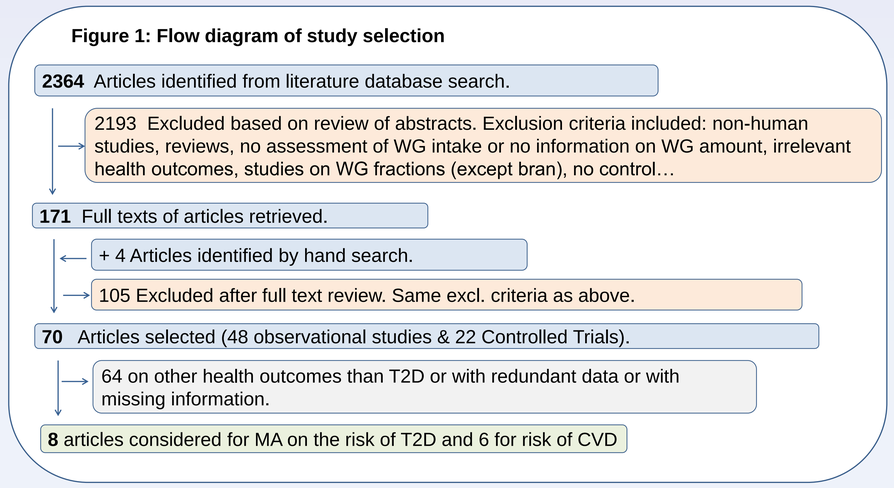
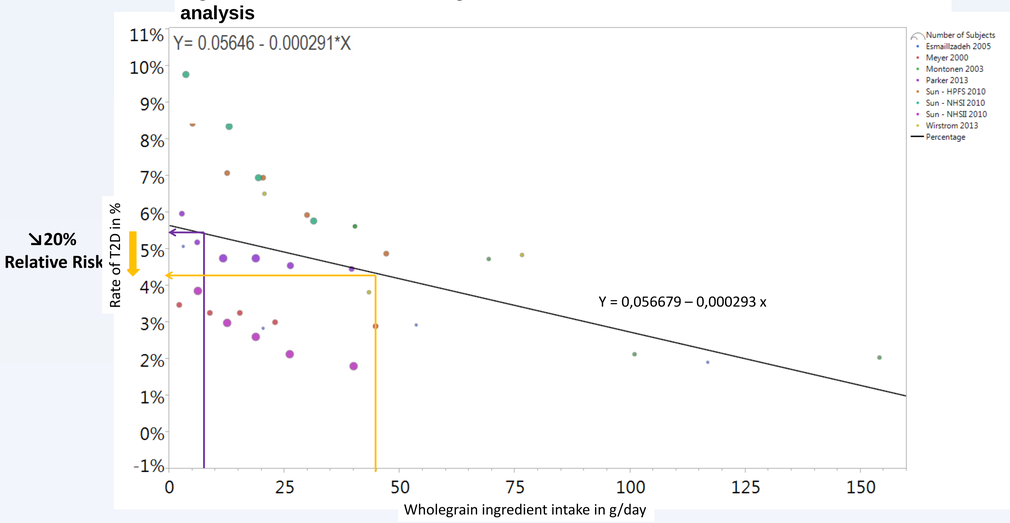


Figure 2: Risk of T2D according to WGI intakes in the 6 studies considered for meta-analysis



Discussion:

- **Increasing WGI intake from 7.5 g/d** (~1/2 serving of WG food) **to 45 g/d** (~3 servings of WG food) would result in a **relative risk reduction of 20%.**
- As a comparison, **lifestyle modifications** regarding diet and exercise such as those applied in the US Diabetes Prevention Program have been shown to **decrease the risk of T2D by ~ 58% in individuals at high risk of T2D**.
- Subjects considered in our MA were not at risk of T2D, and therefore, **a risk reduction of 20%** can be considered as **clinically relevant.**
- The absence of relationship between WGI and CVD risk may be due to a great heterogeneity between studies, to the high influence that each individual study (with its particular characteristics regarding the WG intake level, sex, event rate…) exerts on the results, and a to lack of power (only 4 studies)

Conclusions:

On the 8 studies analyzed, **a clear and statistically significant relationship between WG consumption and occurrence of T2D** has been observed. This suggests that **any increase in WG intake would be beneficial toward the prevention of T2D**. According to the model defined in the meta-analysis, and as an example of calculation, **consuming 45 g/d of WG ingredients (3 servings of WG food) would decrease the relative risk of T2D by 20%** as compared to consuming 7,5 g/d of WG ingredients (a half serving of WG food), which can be considered as **clinically relevant** for a population not at risk of T2D. These data could contribute to set up a **recommended daily intake of WG** and could be **complemented with data on other health outcomes** for which similar analyses are ongoing.

Keywords: wholegrain, dietary intake recommendation, cardiovascular disease, type 2 diabetes