**SHORT TERM SCIENTIFIC MISSION (STSM) – SCIENTIFIC REPORT**

**The STSM applicant submits this report for approval to the STSM coordinator**

**Action number: FA1403**

**STSM title:** Factors affecting the inter-individual variability in cardio-metabolic response to plant food bioactives

**STSM start and end date: 21/Jul/2018 to 01/Sep/2018**

**Grantee name: Manja Zec**

**PURPOSE OF THE STSM**

(max.500 words)

Recent activities of COST FA1403 resulted in several meta-analysis and systematic review papers related to biological response upon consumption of different polyphenol groups. This STSM aimed at capturing and analysing main findings related to COST FA1403 Working Group 2 (WG2) activities regarding the factors influencing inter-individual variability of the cardio-metabolic response upon prolonged consumption of different polyphenol groups. This STSM was structured in bi-directional manner.

**I – Inter-individual variability in the cardio-metabolic response to the polyphenol consumption**

Primary aim of the STSM stay was to address and summarize COST WG2 findings related to factors affecting inter-individual response to the polyphenol consumption. In order to address this question, results from the WG2 papers were extracted. The factors were summarized to include both biological and environmental factors potentially influencing the inter-individual response.

The results from this activity are to be used to further elucidate the factors underlining well-known variability in the cardio-metabolic response upon polyphenol consumption. These factors would lead step forward towards the conclusion on the cardio-metabolic effects of polyphenol consumption within different polyphenol groups. The results also serve as a backbone for the first steps in the creation of public health initiatives and strategies related to practical nutritional advice on polyphenol consumption.

**II – Impact of cocoa and tea flavanols on vascular function: A Meta-Analysis of the existing interventions**

This activity also aimed to strengthen and facilitate delivery of the results and main findings for the primary objective. This secondary objective was to conduct meta-analysis on the effects of consumption of cocoa and tea flavanols on vascular function, specifically systolic and diastolic blood pressure, and endothelial function measured through flow-mediated dilatation. The results obtained through the meta-analyses served as complementary findings for the primary objective, and were the main direction in the line of investigation dealing with factors affecting vascular inter-individual response upon polyphenols consumption, herein specifically flavanols.

The next sections including Description of Work during the STSM and Main Results are outlined according to the primary and secondary objectives.

**DESCRIPTION OF WORK CARRIED OUT DURING THE STSMS**

(max.500 words)

**I – Inter-individual variability in cardio-metabolic response to polyphenol consumption**

In order to address the objective, we summarized the data from the following WG2 papers:

1. Addressing the inter-individual variation in response to consumption of plant food bioactives - towards a better understanding of their role in healthy ageing and cardiometabolic risk reduction (Manach C et al., 2016)
2. Interindividual Variability in Biomarkers of Cardiometabolic Health after Consumption of Major Plant-Food Bioactive Compounds and the Determinants Involved. (Milenkovic D et al., 2017).
3. Impact of Flavanols on Cardiometabolic Biomarkers: a meta-analysis of randomized controlled human trials to explore the role of inter-individual variability. (Menezes R et al., 2017).
4. A Systematic Review and Meta-Analysis of the Effects of Flavanol-Containing Tea, Cocoa and Apple Products on Body Composition and Blood Lipids: Exploring the Factors Responsible for Variability in Their Efficacy (Antonio González-Sarrías et al., 2017)
5. Meta-Analysis of the Effects of Foods and Derived Products Containing Ellagitannins and Anthocyanins on Cardiometabolic Biomarkers: Analysis of Factors Influencing Variability of the Individual Responses. (María-Teresa García-Conesa et al.)

We summarized the factors influencing inter-individual variability in the response:

1. Demographics, including: age, gender, ethnicity, menopausal status
2. Lifestyle, including: BMI, smoking, background diet, adherence to Mediterranean dietary style, physical activity

3. Clinical, including: health status (healthy/at risk/disease), medication use, presence of nutrition-related disorders: overweight, obesity, metabolic syndrome; presence of condition related to cardiovascular risk: hypertension, dyslipidemia
4. Study design, including: type of study, study duration, study country
5. Host-specific, including: genetics and gut microbiota

The cardio-metabolic outcomes which response variability we assessed include but not limited to: serum lipids and vascular function, including: blood pressure and flow-mediated dilatation.

The polyphenol groups of interest were: elagotannins, anthocyanins, flavonols, flavanols.

We additionally explored the variability of the response depending on the polyphenol food source and the study intervention vehicle. Finally, we investigated the most appropriate parameter for quantification and reporting of the inter-individual variability of the response upon polyphenol consumption.

The methodology used in order to address the objective was related to the extraction of the data from the existing meta-analysis and use of data analysis and graphical software in order to explore and present the variability.

**II – Impact of cocoa and tea flavanols on vascular function: A Meta-Analysis**

In order to address the objective, we used the data from the 260 interventions, reported within eligible randomized, controlled studies. Due to the substantial differences in chemical structure between tea and cocoa polyphenols, we *a priori* stratified the studies with regards to the food-based group, and intervention vehicle.

In order to explore clinical significance of the intervention results, we estimated differences in means of the effects in comparison with control. In order to compare effect sizes between different outcomes and/or polyphenol treatments, we also estimated standardized differences in means. In addition to general meta-analysis we performed sub-group meta-analysis based on: sex, age, flavanol dose, study duration, world region, health status, BMI and hypertension baseline status, flavanol source and intervention vehicle.

The effects were analysed by random effects meta-analysis. Fixed model presumes that there is no difference in effects among studies included, except due to the sampling error, which collides main purpose of COST action. Thus, we *a priori* applied random effects meta-analysis. High-risk studies were *a priori* excluded from the analysis, and included for the sensitivity analyses only.

The methodology included advanced statistical analysis and interpretation of the data by means of meta-analysis and single and multiple meta-regressions by use of Comprehensive Meta-Analysis Software.

**DESCRIPTION OF THE MAIN RESULTS OBTAINED**

(max. 500 words)

Herewith presented the most prominent findings.

**I – Inter-individual variability in cardio-metabolic response to polyphenol consumption**

Following graphs represent differences in means in the vascular response and serum lipids, depending on the polyphenol group, food source and other factors.

| Systolic blood pressure | DM (95% CI) | p |
|---|---|---|
| Ellagitannins and Anthocyanins | -1.56 (-2.13, -0.99) | **0.000** |
| Flavonols | -3.05 (-4.83, -1.27) | **0.001** |
| **Diastolic blood pressure** | **DM (95% CI)** | **p** |
| Ellagitannins and Anthocyanins | -1.42 (-2.08, -0.76) | **0.000** |
| Flavonols | -2.63 (-3.83, -1.42) | **0.000** |

***Figure 1.*** **Vascular response to polyphenol group specific intervention.**

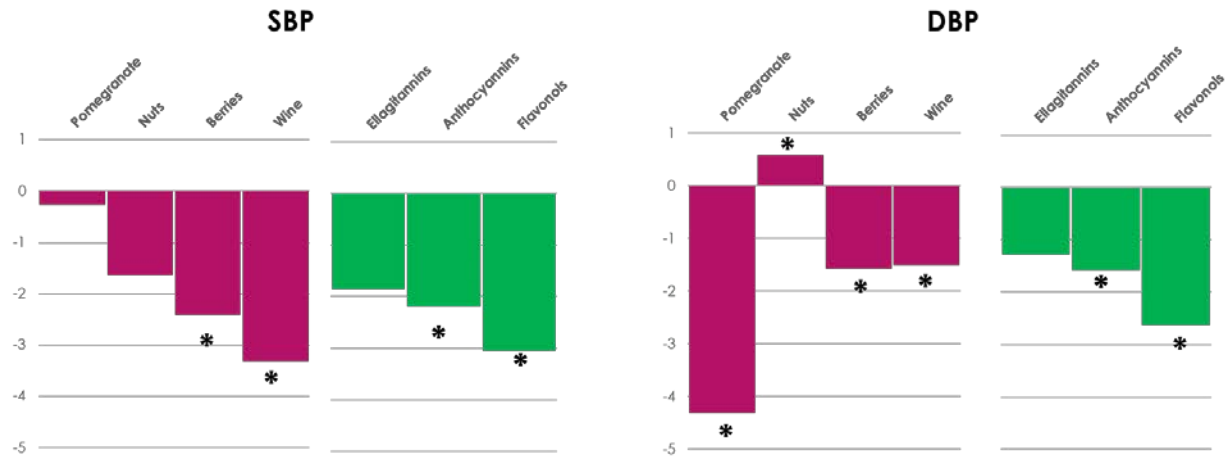


***Figure 2.*** **Variability in BP response (mmHg) based on polyphenol group and food sources.**

**As a summary of the results presented within Figure 2, anthocyanins** and **flavonols** are ***suggested*** to **decrease blood pressure**, in a clinically relevant fashion (decrease of approx 2-3 mmHg). The response variability to **anthocyanin** intake is ***suggested*** to be influenced by food source, with consumption of berries and wine favorably affecting both systolic and diastolic blood pressure, and consumption of pomegranate decreasing diastolic blood pressure only. Suggested adverse effect of nut consumption on diastolic blood pressure, together with pomegranate effect need to be considered in light of small number of available studies.

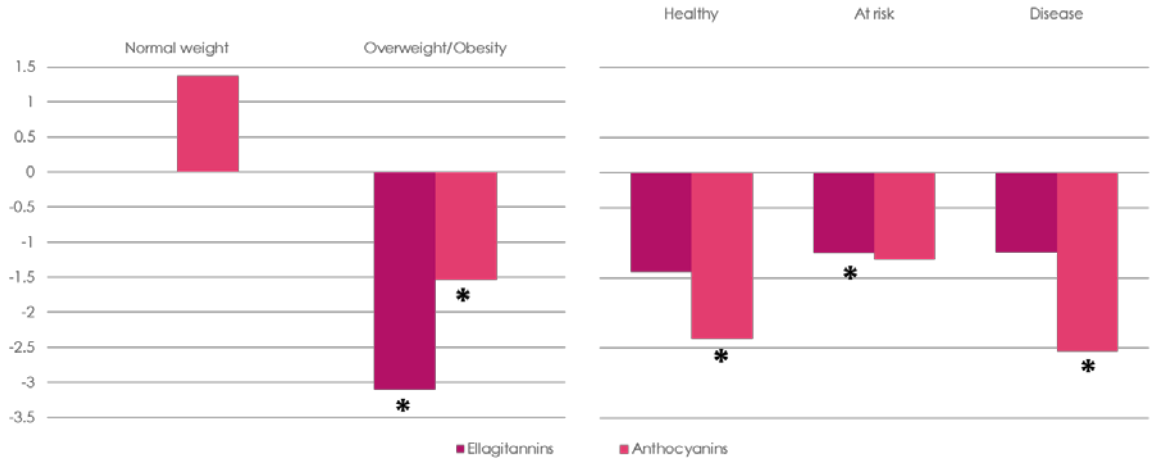


***Figure 3.*** **Variability in SBP response (mmHg) based on BMI and health status.**

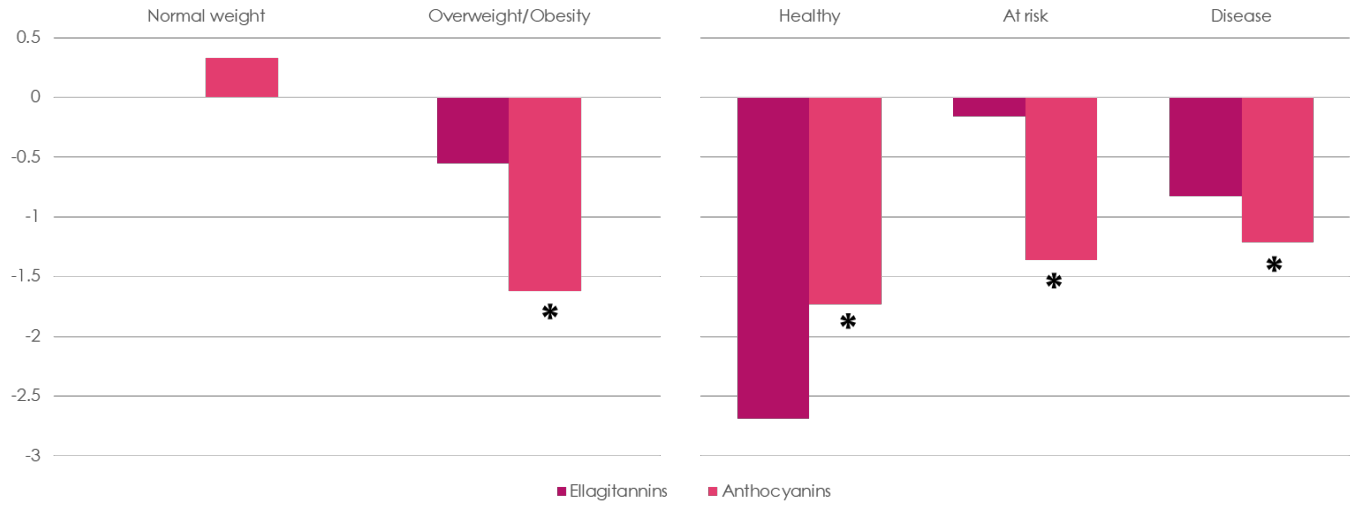


***Figure 4.*** **Variability in DBP response (mmHg) based on BMI and health status.**

Based on the Figure 3 and 4, we conclude that **ellagitannins and anthocyanins** are ***suggested*** *to* decrease systolic blood pressure in subjects with higher BMI values. **Anthocyanins** are ***suggested*** to **decrease systolic blood pressure** in healthy and subjects with chronic conditions. In subjects with normal weight, **anthocyanins** appear to non-significantly increase systolic blood pressure. **Anthocyanins** are ***suggested*** *to* decrease diastolic blood pressure in subjects with higher BMI values. **Anthocyanins** are ***suggested*** to **decrease diastolic blood pressure** independently on the other CVD risk factors. In subjects with normal weight, **anthocyanins** appear to non-significantly increase diastolic blood pressure.

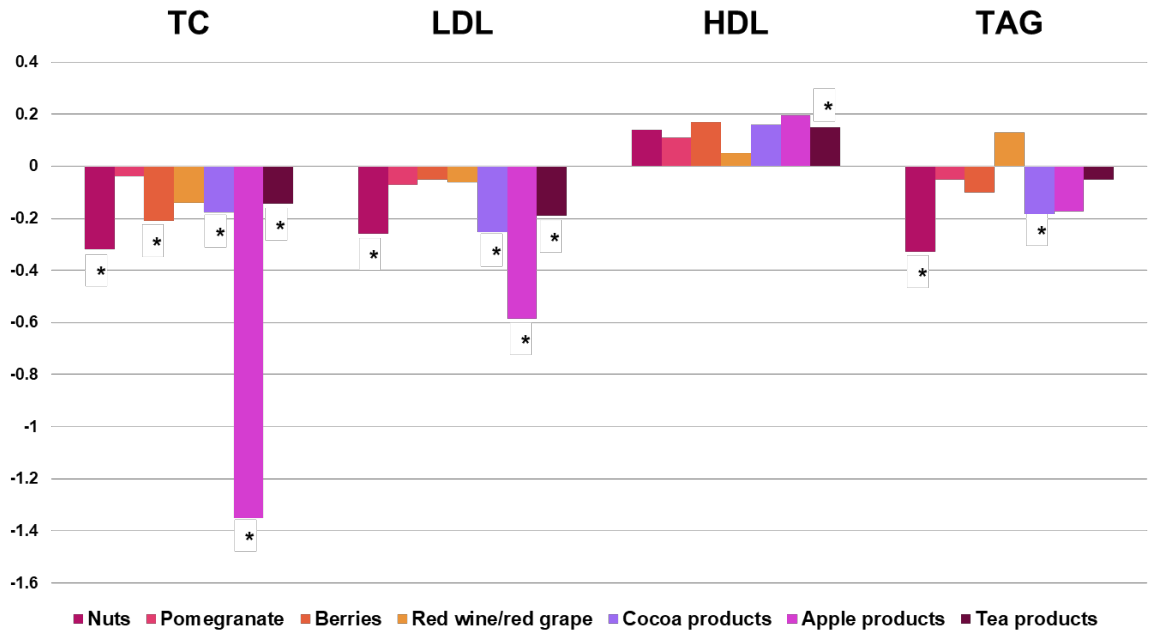


***Figure 5.*** **Polyphenol food source affecting interi-ndividual response in serum lipid biomarkers.**

Based on the Figure 5, we conclude that polyphenol from different food sources exert effects on serum lipids, with apple products appearing to exert the most prominent effect.

**Possible ways of quantifying variability of the outcomes**

We explored the most plausible biomarkers to quantify the variability in the response. Based on the meta-analysis results we are able to conclude on the between-study (i.e. inter-study) variability, and not inter-individual variability, since the mean differences (standardized or not) and dispersion parameters obtained within the metas are calculated based on the *per study* data and not individual data. However, if we consider constraint meta-analysis inclusion criteria for the tightly controlled RCTs, we assume that results from the single study are representative of the corresponding population, and might be extrapolated to the individuals participating the study. Similarly, results obtained within the meta-analysis are representative of the studies selected to be included in the meta. This way the results from the meta-analysis, might be translated at the individual level.

Regarding parameters we might exploit to decipher the variability, the following are of importance:

- **Coefficient of variation**, calculated per outcome, per factor (either within or between subgroup), by use of the Mean differences and SDs estimated from the meta-analysis.

- **I-squared**: is the percentage of variability among studies due to the heterogeneity among studies. This is a relative parameter largely based on the study design or any other study-specific and non-intervention specific induced variability, which imposes the variability among studies.

- **Tau-squared** is an absolute measurement of the effect size variability, as reported previously *(Deeks et al 2008, Borenstein et al 2009*). The link between I-sq and Tau-sq is in the fact that I-sq is calculated as ratio between total variability and total heterogeneity as absolute values.

- **R-squared**, is percentage of the variability of the effect due to the certain predictor (wither continuous or group).

To conclude, Tau-squared is an absolute measure and depicts the variance of the effect size and might be used to compare between-group variance of cardio-metabolic response depending on specific biological/lifestyle factor. R-squared is relative measure and depicts the amount of variability among studies (or subgroups), that might be ascribed to particular predictor. The tau-squared is proposed as a plausible tool for measuring inter-individual variability in the cardio-metabolic response.

**II – Impact of cocoa and tea flavanols on vascular function: A Meta-Analysis of the existing interventions**

Prolonged consumption of cocoa flavanols is associated with clinically significant decrease in SBP (DM= -3.41; 95%CI: -4.25/-2.57) and DBP (DM= -3.44; 95%CI: -5.01/ -1.87). The consumption of cocoa flavanols increased flow-mediated dilatation (DM= 1.18; 95%CI: 0.94/ 1.41). The 100%, 13% and 38% of the variability of vascular response were explained by the model containing flavanol dose in mg, study duration in weeks and baseline hypertension status, and measured by R-squared parameter.

The main findings and graphs from the meta-analysis are presented in the continuation.

Note: Some of the results are still under analysis, and will be presented accordingly in a timely manner.

| | Difference in means | Standard error | Lower limit | Upper limit | p-Value | Relative weight |
|---|---|---|---|---|---|---|
| Almoosawi 2012 a | -4.980 | 2.420 | -9.723 | -0.237 | 0.040 | 1.34 |
| Almoosawi 2012 b | -2.450 | 2.697 | -7.736 | 2.836 | 0.364 | 1.13 |
| Babar 2018 | -0.230 | 1.443 | -3.058 | 2.598 | 0.873 | 2.66 |
| Bajerska 2015 | -4.800 | 4.071 | -12.778 | 3.178 | 0.238 | 0.56 |
| Bingham 1997 | -0.200 | 3.931 | -7.905 | 7.505 | 0.959 | 0.59 |
| Bogaard 2010 | -1.400 | 2.690 | -6.672 | 3.872 | 0.603 | 1.14 |
| Bogdanski 2012 | -4.000 | 2.500 | -8.900 | 0.900 | 0.110 | 1.27 |
| Brown 2009 | -2.590 | 1.648 | -5.820 | 0.640 | 0.116 | 2.28 |
| Brown 2011 | -0.300 | 0.968 | -2.197 | 1.597 | 0.757 | 3.79 |
| Chen 2015 | -2.400 | 4.698 | -11.608 | 6.808 | 0.609 | 0.43 |
| Crews 2008 | -0.530 | 2.859 | -6.134 | 5.074 | 0.853 | 1.03 |
| Davison 2008 | -6.100 | 3.182 | -12.336 | 0.136 | 0.055 | 0.86 |
| Davison 2010 a | -1.200 | 4.299 | -9.626 | 7.226 | 0.780 | 0.50 |
| Davison 2010 b | -0.900 | 4.090 | -8.917 | 7.117 | 0.826 | 0.55 |
| Davison 2010 c | -2.000 | 4.532 | -10.883 | 6.883 | 0.659 | 0.46 |
| Desch 2010 | -0.600 | 2.237 | -4.985 | 3.785 | 0.789 | 1.51 |
| Desideri 2012 a | -8.700 | 2.521 | -13.640 | -3.760 | 0.001 | 1.26 |
| Desideri 2012 b | -6.800 | 2.477 | -11.654 | -1.946 | 0.006 | 1.29 |
| Dower 2015 | -0.700 | 2.985 | -6.551 | 5.151 | 0.815 | 0.96 |
| Engler 2004 | -1.800 | 5.629 | -12.832 | 9.232 | 0.749 | 0.31 |
| Esser 2014 | -1.000 | 1.881 | -4.686 | 2.686 | 0.595 | 1.93 |
| Esser 2018 | -0.450 | 2.746 | -5.832 | 4.932 | 0.870 | 1.10 |
| Flammer 2012 | -7.400 | 7.100 | -21.315 | 6.515 | 0.297 | 0.20 |
| Fraga 2005 | -4.000 | 3.742 | -11.334 | 3.334 | 0.285 | 0.65 |
| Frank 2009 | -1.000 | 4.721 | -10.253 | 8.253 | 0.832 | 0.42 |
| Grassi 2005 (I) a | -11.000 | 1.779 | -14.486 | -7.514 | 0.000 | 2.07 |
| Grassi 2005 (I) b | -6.200 | 2.750 | -11.590 | -0.810 | 0.024 | 1.10 |
| Grassi 2015 a | -4.100 | 2.542 | -9.083 | 0.883 | 0.107 | 1.24 |
| Grassi 2015 b | -7.700 | 2.542 | -12.683 | -2.717 | 0.002 | 1.24 |
| Grassi 2015 c | -6.900 | 2.542 | -11.883 | -1.917 | 0.007 | 1.24 |
| Grassi 2015 d | -8.100 | 2.542 | -13.083 | -3.117 | 0.001 | 1.24 |
| Heiss 2010 | -3.000 | 1.414 | -5.772 | -0.228 | 0.034 | 2.72 |
| Heiss 2015 a | -4.000 | 3.742 | -11.334 | 3.334 | 0.285 | 0.65 |
| Heiss 2015 b | -3.000 | 4.472 | -11.765 | 5.765 | 0.502 | 0.47 |
| Hodgson 2002 | -1.000 | 6.769 | -14.267 | 12.267 | 0.883 | 0.21 |
| Hodgson 2003 | -1.000 | 6.164 | -13.082 | 11.082 | 0.871 | 0.26 |
| Hsu 2008 | -0.700 | 3.819 | -8.184 | 6.784 | 0.855 | 0.62 |
| Hsu 2011 | -7.000 | 4.747 | -16.303 | 2.303 | 0.140 | 0.42 |
| Ibero-Baraibar 2014 | -1.000 | 3.919 | -8.682 | 6.682 | 0.799 | 0.60 |
| Kafeshani 2017 a | -2.820 | 3.022 | -8.744 | 3.104 | 0.351 | 0.94 |
| Kafeshani 2017 b | -7.190 | 2.731 | -12.542 | -1.838 | 0.008 | 1.11 |
| Kajimoto 2003 a | -0.500 | 5.096 | -10.488 | 9.488 | 0.922 | 0.37 |
| Kajimoto 2003 b | -4.900 | 4.841 | -14.388 | 4.588 | 0.311 | 0.41 |
| Kajimoto 2003 c | -8.200 | 4.882 | -15.766 | 3.366 | 0.204 | 0.40 |
| Khan 2012 | -3.000 | 5.464 | -13.710 | 7.710 | 0.583 | 0.32 |
| Koli 2015 | -1.000 | 3.151 | -7.177 | 5.177 | 0.751 | 0.87 |
| Liu 2014 | -3.600 | 3.321 | -10.109 | 2.909 | 0.278 | 0.80 |
| Livia de P. Nogueira 2016 | -4.660 | 0.332 | -5.311 | -4.009 | 0.000 | 5.46 |
| Maeda-Yamamoto 2018 a | -0.400 | 2.756 | -5.802 | 5.002 | 0.885 | 1.09 |
| Maeda-Yamamoto 2018 b | -4.200 | 2.866 | -9.817 | 1.417 | 0.143 | 1.02 |
| Massee 2015 | -6.290 | 3.304 | -12.766 | 0.186 | 0.057 | 0.81 |
| Mastroiacovo 2015 a | -6.200 | 1.804 | -9.735 | -2.665 | 0.001 | 2.04 |
| Mastroiacovo 2015 b | -5.200 | 1.864 | -8.854 | -1.546 | 0.005 | 1.95 |
| Mellor 2010 | 0.000 | 7.483 | -14.667 | 14.667 | 1.000 | 0.18 |
| Miyazaki 2013 | -4.100 | 6.262 | -16.374 | 8.174 | 0.513 | 0.25 |
| Mogollon 2013 a | -1.100 | 2.264 | -5.537 | 3.337 | 0.627 | 1.48 |
| Mogollon 2013 b | -0.800 | 2.659 | -6.011 | 4.411 | 0.763 | 1.16 |
| Monagas 2009 | -3.000 | 5.176 | -13.144 | 7.144 | 0.562 | 0.36 |
| Muniyappa 2008 | -1.000 | 3.742 | -8.334 | 6.334 | 0.789 | 0.65 |
| Murphy 2003 | -1.000 | 4.006 | -8.852 | 6.852 | 0.803 | 0.57 |
| Nagao 2007 | -2.700 | 1.659 | -5.951 | 0.551 | 0.104 | 2.26 |
| Nagao 2009 a | -2.000 | 4.067 | -9.971 | 5.971 | 0.623 | 0.56 |
| Nagao 2009 b | -2.300 | 4.054 | -10.246 | 5.646 | 0.570 | 0.56 |
| Nagao 2009 c | -2.100 | 4.265 | -10.459 | 6.259 | 0.622 | 0.51 |
| Nantz 2009 a | -5.000 | 1.204 | -7.359 | -2.641 | 0.000 | 3.18 |
| Nantz 2009 b | -3.000 | 1.168 | -5.288 | -0.712 | 0.010 | 3.27 |
| Neufingerl 2013 | -0.000 | 7.968 | -15.617 | 15.617 | 1.000 | 0.16 |
| Njike 2011 | -2.300 | 2.410 | -7.023 | 2.423 | 0.340 | 1.35 |
| Ottaviani 2015 | -1.000 | 2.792 | -6.473 | 4.473 | 0.720 | 1.07 |
| Ried 2009 | -3.000 | 6.196 | -15.144 | 9.144 | 0.628 | 0.25 |
| Rostami 2015 | -5.340 | 2.547 | -10.331 | -0.349 | 0.036 | 1.24 |
| Rull 2015 | -1.000 | 2.557 | -6.012 | 4.012 | 0.696 | 1.23 |
| Sansone 2015 | -4.000 | 2.646 | -9.186 | 1.186 | 0.131 | 1.17 |
| Sone 2011 | 0.000 | 4.500 | -8.821 | 8.821 | 1.000 | 0.46 |
| Suliburska 2012 | -1.310 | 2.077 | -5.380 | 2.760 | 0.528 | 1.68 |
| Taubert 2007 a | -0.500 | 0.498 | -1.476 | 0.476 | 0.315 | 5.09 |
| Taubert 2007 b | -2.800 | 0.503 | -3.786 | -1.814 | 0.000 | 5.07 |
| Taubert 2007 c | -3.000 | 0.482 | -3.946 | -2.054 | 0.000 | 5.13 |
| Tzounis 2011 | -2.800 | 3.540 | -9.739 | 4.139 | 0.429 | 0.71 |
| Wang-Polagruto 2008 | -16.000 | 11.081 | -37.717 | 5.717 | 0.149 | 0.08 |
| Widlansky 2007 | 0.000 | 4.662 | -9.138 | 9.138 | 1.000 | 0.43 |
| | -3.180 | 0.320 | -3.806 | -2.553 | 0.000 | |

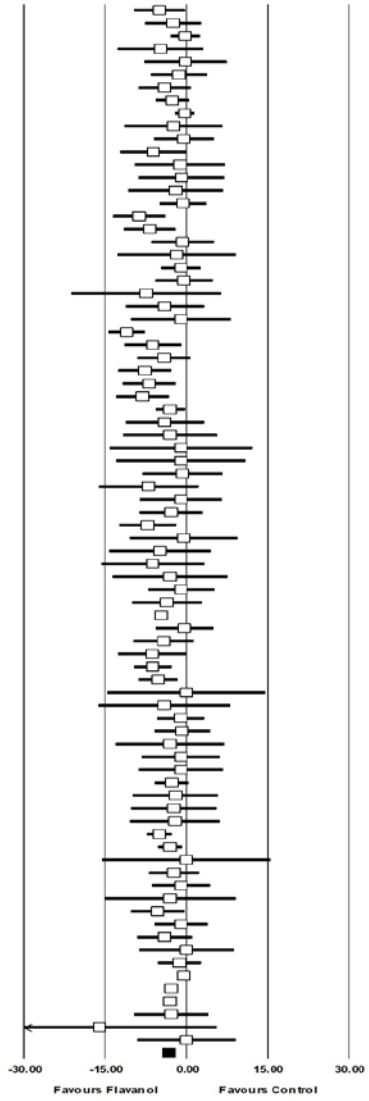


**Figure 6. Intervention effects of flavanol consumption from different food sources on systolic blood pressure.**

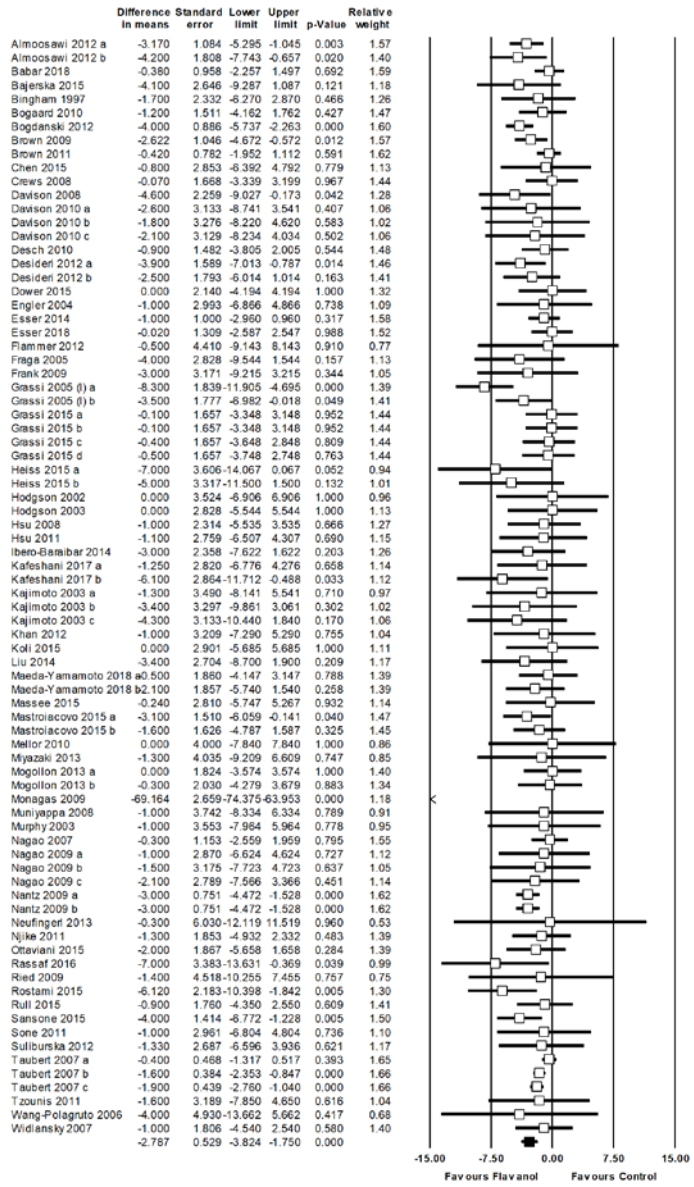


**Figure 7. Interventional effects of flavanol consumption from different food sources on diastolic blood pressure.**

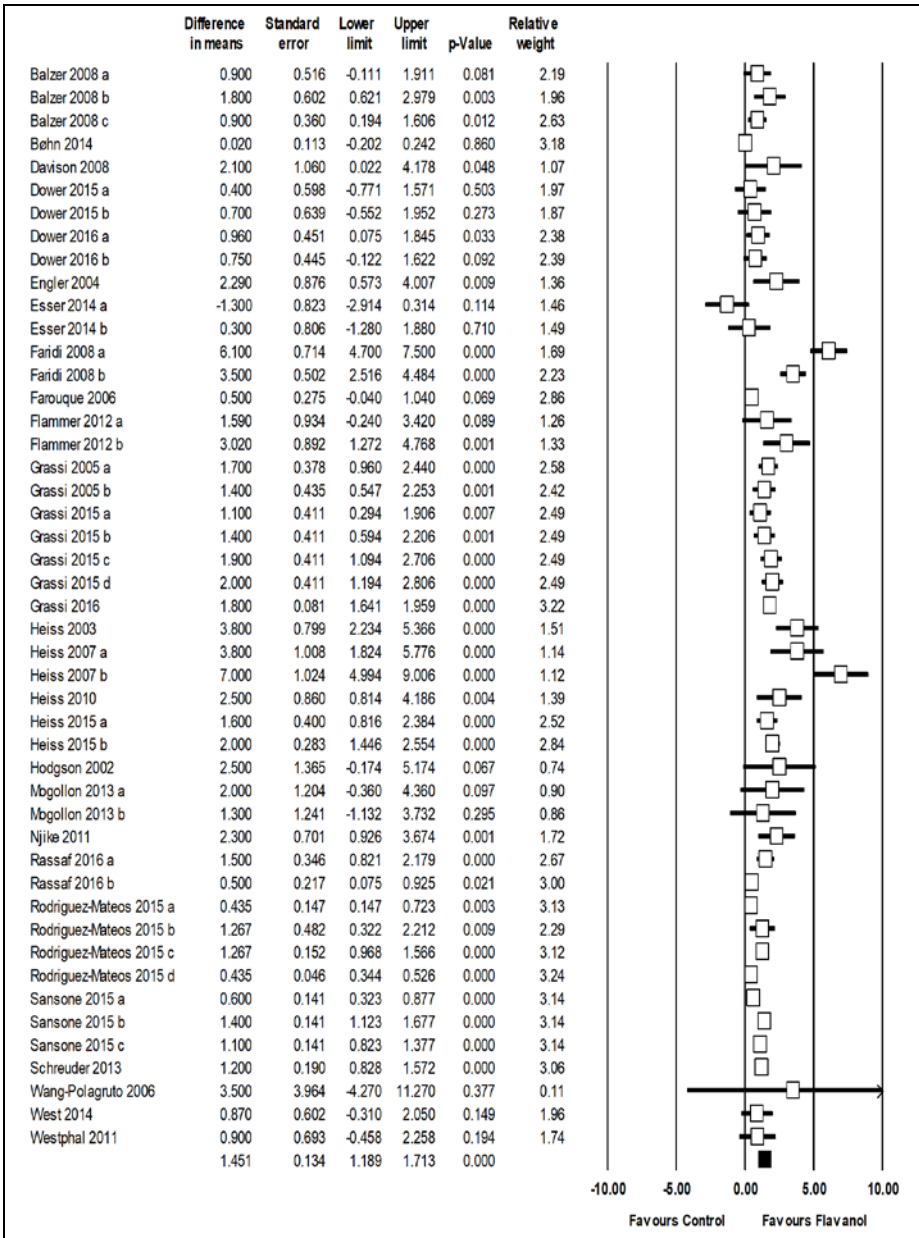


**Figure 8. Interventional effects of flavanols consumption from different food sources on flow-mediated dilatation.**

## FUTURE COLLABORATIONS

(max.500 words)

The results obtained within the STSM would strengthen overall COST FA1403 network. Those results enable umbrella overview of the main findings within the COST Working Group 2 activities and related to inter-individual variability in the cardio-metabolic response related to polyphenol intake. Future collaboration will be aimed at the confirmation of the results obtained within the STSM, as well as translating the scientific results obtained within the STSM into the message aimed at targeted groups and stakeholders, and finally general public. Specifically, we aim at additionally performing meta-analysis of the selected interventions within studies dealing with the health effects of specifically either tea or cocoa. Finally, we aim at

incorporating the results from the meta-analysis in the final overview of the factors affecting inter-individual variability of the cardio-metabolic response upon polyphenol consumption.

Of utmost importance, recent results indicate that we are eventually able to tackle inter-study variability *per se*. Future actions should be directed towards conjoint platform for the reporting of the data from nutritional polyphenol interventions, that would enable analyse and interpretation of the individual response to the interventions, and eventually inter-individual variability in the response.

Future collaboration will be aimed at further elucidation of the factors driving inter-individual response in cardio-metabolic response upon polyphenol consumption, addressing nutrigenetic implications of polyphenol intake related to different cardio-metabolic response.

We anticipate that the results would serve as a backbone platform for the future research and initiatives in the field of polyphenol research, and aimed at public health strategies related to the directed recommendations for the food-based polyphenols intake for the sustainable cardio-metabolic health within different population groups. Additionally, we believe the results would serve as the direction for the future good-research practice related to conduction and reporting of the results from the clinical studies related to the consumption of different polyphenol groups.

In addition, the results enabled the collaboration within Prof Rodriguez's and Dr Zec's research groups within KCL and IMR, respectively, that would serve the purpose of the future research related to the clinical and eventually epidemiological implications of flavanol intake and vascular function.