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Title page

Adherence to UK dietary guidelines is associated with higher dietary intakes of total and specific polyphenols compared to a traditional UK diet: further analysis of data from the CRESSIDA randomised controlled trial.

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Keywords: polyphenols, dietary intake, dietary guidelines, randomised controlled trial

Abstract

Adherence to dietary guidelines may result in higher intakes of polyphenols via increased consumption of fruits, vegetables and whole grains. We compared polyphenol dietary intakes and urinary excretion between two intervention groups in the CRESSIDA study: a 12-week, parallel-arm, randomised controlled trial (n=161; 64 M, 97 F; aged 40-70 y). One group adhered to UK dietary guidelines (DG) whereas the other group consumed a representative UK diet (control). We estimated polyphenol dietary intakes, using 4-day food diaries (4-DFD) and food frequency questionnaires (FFQ), and analysed twenty-four hour polyphenol urinary excretion by LC-MS/MS on a subset of participants (n=46 control; n=45 DG). A polyphenol food composition database for 4-DFD analysis was generated using Phenol-Explorer and USDA databases. Total polyphenol intakes by 4-DFD at endpoint (geometric means with 95% CI, adjusted for baseline and gender) were significantly higher in the DG group (1279 mg/d/10 MJ; 1158, 1412) compared to the control group (1084 mg/d/10 MJ; 980, 1197). The greater total polyphenol intakes in the DG group were attributed to higher intakes of anthocyanidins, proanthocyanidins and hydroxycinnamic acids, with the primary food sources being fruits, cereal products, nuts and seeds. FFQ estimates of flavonoid intakes also detected greater intakes in DG compared with the control group. Twenty-four hour urinary excretion showed consistency with 4-DFD in their ability to discriminate between dietary intervention groups for 6 out of 10 selected, individual polyphenols. In conclusion, following UK dietary guidelines increased total polyphenol intakes by approximately 20%, but not all polyphenol subclasses corresponded with this finding.

Introduction

Greater consumption of fruit and vegetables and whole grains is associated with reduced risk of chronic diseases[1, 2, 3, 4, 5]. Increased intakes of different components present in these food groups, like fibre[6], micronutrients[7] and polyphenols[8], have been identified as being partly responsible for beneficial effects. However, results from the UK National Diet and Nutrition Survey (NDNS) rolling programme[9, 10, 11] reveal that consumption of fruit and vegetables and whole grains is below recommended intakes in at least 70% of the UK adult population [9, 10, 11, 12]. Dietary polyphenols are a diverse range of phytochemicals containing 1 or more aromatic rings attached to a hydroxyl group. The term "polyphenol" commonly encompasses phenolic acids, flavonoids, stilbenes and lignans, which are derived from a wide range of plant foods including fruits, vegetables, and cereals. However, beverages such as tea, coffee, red wine, and fruit juices represent the main dietary sources[13]. Epidemiological studies have shown a negative relationship between consumption of polyphenols and cardiovascular disease[14, 15, 16, 17, 18], cancer[19, 20, 21, 22] and type 2 diabetes [18, 23, 24, 25, 26]. Multiple mechanisms have been identified that may contribute to any direct causal relationship between dietary polyphenols and prevention of chronic diseases, including modulating inflammatory pathways, exerting effects on oxidative signalling and enzyme activity, and regulation of gene expression[8].

Previous reports in UK populations, using either 24 h recall[27, 28, 29, 30, 31] or food diaries[27, 28, 29, 30, 31] , suggest that habitual polyphenol intakes are in the range of 800-1600 mg/d, depending on the population studied. However, the use of different dietary assessment methods, food polyphenol composition databases, and gaps in polyphenol composition data for certain foods limit the reliability of current intake estimates in various countries[32] . Food diaries may provide a relatively accurate estimate of polyphenol intake and are more suitable for dietary intervention studies with smaller study populations, but they reflect short-term intakes rather than habitual consumption patterns, which could be particularly misleading for seasonally available foods[33]. Research groups have designed and validated FFQs to estimate dietary flavonoid intake in different populations[34, 35], which may provide more reliable habitual intake estimations for specific populations. However, these remain unavoidably susceptible to bias due to self-reporting errors, portion size quantification and estimation errors resulting from the lack of data on polyphenol content in food [36]. Whichever dietary assessment method is selected, the resulting intake data will only be accurate if the polyphenol composition of foods database is fit for purpose. At present, the most commonly used food polyphenol composition

databases are Phenol-Explorer[37, 38, 39], which provides information on the content of 502 polyphenols (of the 4 classes) in 459 food items including aglycones, glycosides, and esters, and the USDA databases[40, 41, 42] which includes 35 flavonoids (aglycones only) in 506 food items, respectively. Urinary excretion of polyphenols has been shown to be a suitable biomarker for the intake of polyphenols[43, 44], fruit and vegetables[45, 46], polyphenol-rich beverages[47, 48] and polyphenol-rich food[49, 50]. The presence of polyphenol metabolites in urine is closely related to the quantity consumed and overall metabolism in the body. However, different polyphenols can produce common metabolites and so the biomarker selected must reflect the specific intake of the parent polyphenol in question in order to accurately estimate intakes of individual phenolic compounds[51].

Dietary guidelines in the UK are population-based recommendations for maintenance of health and wellbeing, and to reduce risk of chronic diseases. No dietary recommendations exist for polyphenols, although the advantages and disadvantages of this approach have been debated[52, 53, 54]. A dietary pattern consistent with current dietary guidelines could reasonably be assumed to be richer in polyphenols than the average UK dietary pattern due to increased intakes of fruit and vegetables and whole grains. However, not all fruits and vegetables are polyphenol-rich[55], and in fact the majority of dietary polyphenols in the UK are provided by tea, coffee, and cocoa intakes[30]. The aim of this study was to compare dietary polyphenol intakes in a free-living study population randomised to either following UK dietary guidelines, or consuming a representative, more traditional UK diet. The hypothesis was that adherence to UK dietary guidelines would result in an increase in total dietary polyphenol intakes compared with a diet that was more representative of the UK adult population. The primary outcome variable was total polyphenol intake, adjusted for energy intake, assessed by 4-day food diary. Secondary outcome variables included intakes of classes, subclasses and individual phenolic acids/polyphenols. Data were also compared with FFQ[15], and biomarkers of polyphenol intake (24 h excretion of representative urinary metabolites).

Methods

Study design

The Cardiovascular risk REduction Study: Supported by an Integrated Dietary Approach (CRESSIDA) was a 12-week parallel-designed, randomised, controlled trial funded by the Food Standards Agency/Department of Health (UK) (N02047), sponsored by King's College London. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures

involving human subjects were approved by the St. Thomas' Hospital Research Ethics Committee (10/H0802/24)[56]. Written informed consent was obtained from all subjects. This trial was registered at Current Controlled Trial (http://www.controlled-trials.com/ISRCTN) as ISRCTN92382106. The primary aim of the original study[56] was to assess effects on CVD risk factors when following a diet based on UK dietary guidelines (DG) in comparison to a representative UK diet (control). A sample size of 78/group had 90% power to detect a 4 mm Hg effect of diet on daytime systolic ambulatory blood pressure (alpha 0.05); this sample size was also large enough to detect a 5% change in the ratio of total cholesterol (TC):HDL cholesterol and a 1% unit change in flow-mediated dilatation of the brachial artery with sufficient statistical power. The results of these primary outcomes have been published previously[56].

The data presented here comprises a secondary analysis of dietary intake data from both the DG and control groups at baseline and endpoint of the 12-week dietary intervention period, to determine whether adherence to UK dietary guidelines results in an increase in polyphenol intake.

Participants

Healthy men and women [BMI (in kg/m^2) ≥18.5 and ≤35] were recruited from the London area (August 2010–July 2012) by newspaper (London Metro) and electronic advertisement (King's College London e-mail and website). Participants between the age of 40-70 y were chosen because risk increases markedly with age and an upper age limit of 70 y was selected because absolute annual risk of CVD exceeds 2% beyond that age in the majority of people, and a higher proportion are receiving medication on daily basis. A full list of inclusion and exclusion criteria has been reported previously[56]. For randomisation a purpose-designed clinical database was used (MedSciNet AB, Stockholm, Sweden), which undertook the minimisation randomisation, balancing the treatment arms for the minimisation variables of gender, age and ethnicity[56]. Participants received dietary advice in person at baseline and at week 4, and by phone at week 6 and 8. Dietary assessment included two FFQ and two four-day food diaries (4-DFD) administered at baseline and endpoint and two 24-h recalls administered at weeks 4 and 8. Urine samples were collected at four time points; baseline, week 4, 8 and endpoint.

Dietary advice

Participants randomised to the DG group were advised to increase fruit and vegetables intake to 5 portions/day; whole grains intake to >50% of cereal intake; to consume 2 portions of fish per week (1 of which should be oily); to replace full-fat with reduced fat dairy products; to replace fats rich in

saturated fatty acids with spreads/oils low in saturated fatty acids and high in monounsaturated fatty acids; to restrict salt intake to <6 g/d (<100 mmol/d) and to reduce intake of free sugars. The control diet comprised a nutritionally balanced, traditional UK diet, formulated with familiar foods (full cream milk, cheese, butter, meat and meat products, non-wholegrain cereals), reflecting typical UK intakes of fruit and vegetables (3 portions/d), with a higher content of saturated fatty acids (14% energy), unrestricted intakes of salt and sugar, and low intakes of oily fish. The study included provision of spread, oil, whole grain pasta, rice and cereal bars, minimally processed wholegrain breakfast cereal (oats, muesli, etc.), almonds and macadamia nuts and tinned oily fish to the intervention group and spread, oil and refined cereals as pantry items to the control group. Participants of both groups were instructed to refrain from taking nutritional supplements during the study[57].

Four-day food diary (4-DFD)

Dietary intake of polyphenols was quantified from 4-DFD, at baseline and endpoint of the 12-wk intervention. A polyphenol food composition database was generated using Phenol-Explorer[37, 38, 39] and USDA databases[40, 41, 42], and extended using polyphenol retention factors and recipes provided by participants. If a recipe was not provided by a participant, a standard recipe was obtained from either the UK food tables[58], a UK food industry recipe book[59], the BBC Good Food website[60] or additional websites specialised in UK recipes and other countries' typical cuisines. In total 118 recipes were obtained from participants, 93 from UK food tables, 20 from a UK food industry recipe book, 78 from the BBC Good Food website and 94 from other websites. Polyphenol intake was estimated for four classes of polyphenols: flavonoids, phenolic acids, lignans and stilbenes. An additional group of polyphenols were included under the name "other polyphenols"; since Phenol-Explorer grouped a series of compounds including alkylmethoxyphenols, alkylphenols, curcuminoids, furanocoumarins and tyrosols. The flavonoid intake was analysed in eight subclasses: anthocyanins, dihydrochalcones, flavanols (flavan-3-ols monomers and theaflavins), proanthocyanidins, flavanones, flavones, flavonols and isoflavones, for each subclass a range of 2 to 11 of the most representative individual compounds were selected. For phenolic acids subclass 2 groups were analysed: hydroxybenzoic acids and hydroxycinnamic acids, for each group a range of 4 to 6 of the most representative individual compounds were selected. For lignans subclass, 4 individual compounds were analysed: pinoresinol, lariciresinol, secoisolariciresinol and matairesinol. For stilbenes subclass, resveratrol was selected and analysed. A total of 52 individual polyphenols were analysed and 1141 food items were included in the final database.

Food frequency questionnaires (FFQ)

Dietary intake of flavonoids was quantified from FFQ (EPIC-Norfolk FFQ v.6) [61] at baseline and endpoint of the 12-wk intervention. Flavonoid intake was estimated from 6 subclasses and most representative compounds for each: flavanones (hesperetin, naringenin, eriodictyol), anthocyanins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin), flavones (apigenin, luteolin), flavonols (quercetin, kaempferol, myricetin, isorhamnetin), flavan-3-ols (catechin, epicatechin, gallocatechin, epigallocatechin, epicatechin-3-gallate, epigallocatechin-3-gallate) and polymers (theaflavins, thearubigins and proanthocyanidins). In total 32 individual flavonoids were analysed using a database created and kindly provided by Dr Amy Jennings and Prof Aedin Cassidy at University of East Anglia[15] and modified for the requirements of the FFQ analysis, so that the flavonoid content of 130 food items were analysed. FFQ registers the frequency of consumption of specific foods, of standard portion size, in a month. There were nine answer options which varied from "never or less than once in a month" to "six or more per day". To calculate the total intake of subclasses of flavonoids, frequencies were converted to daily portions and multiplied by flavonoid content in each specific food item; the results were summed for each subclass and for each participant.

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

Twenty-four hour urine collections were made as previously described[56], using boric acid as preservative[62] and aliquots stored at -80 ºC until analysis. Completeness of urine collection was measured using recovery of para-aminobenzoic acid according to a standard protocol[63]. LC-MS/MS analysis was only performed on endpoint urine samples, collected at week 12 of the intervention to coincide with dietary assessment by 4-DFD. A previously published protocol for polyphenol analysis in urine[47] was adapted and developed for the quantification of ten aglycone metabolites of polyphenols. A subsample of the CRESSIDA study was selected for the analysis; the selection was based on the fruit and vegetables (F&V) intake reported in the endpoint FFQ, subsample included participants in the control group reporting the lowest intakes of F&V, and participants in the intervention group reporting the highest intakes of F&V were analysed. Quantification of endpoint samples allowed the comparison between groups at the end of the dietary intervention; the aim was to detect greater amounts of polyphenols excreted in urine by participants who reported consuming the most polyphenols by FFQ compared to participants who reported consuming the least, and to determine agreement with food diary data. One or two of the most representative aglycones of different polyphenol subclasses were selected for quantification. Ten phenolic compounds were analysed; phloretin (dihydrochalcones),

epicatechin (flavan-3-ols), hesperetin and eriodictyol (flavanones), luteolin (flavones), quercetin (flavonols), daidzein (isoflavones), gallic and vanillic acid (phenolic acids) and enterolactone as a product of microbial metabolism of lignans in colon. The phenolic compounds selected for quantification have been suggested as suitable biomarkers of polyphenol intake[55] with a high recovery and good correlation with fruit and vegetable intakes when estimated by FFQ, 24-h recalls or food diaries[50]. The major food sources of the ten phenolic compounds are fruit, vegetables and wholegrain products, or represent the main metabolites of parent glucosides present in the previously mentioned foods.

Purified standards phloretin, epicatechin, eriodictyol, hesperetin, luteolin, daidzein, gallic and vanillic acids were obtained from Santa Cruz Biotechnology, Germany and quercetin, enterolactone and catechin-2, 3, 4-$^{13}C_3$ from Sigma-Aldrich, UK. Stock solutions were prepared for all the purified phenolic compounds, two milligrams of each of the ten purified compounds were diluted in one millilitre of methanol or dimethyl sulfoxide according to supplier specifications and one milligram of Catechin-2, 3, 4-$^{13}C_3$ (internal standard) in one millilitre of methanol. Stock solutions were stored at -40 ^{o}C or -80 ^{o}C (internal standard). Enzyme β-glucuronidase/sulfatase (0.05 g) type H-5 from *Helix Pomatia* (Sigma-Aldrich, UK) was diluted in one millilitre of 0.2% sodium chloride solution to create a working solution of 50,000 units per millilitre; the enzyme solution was stored at -40 ^{o}C. Urine samples (250 µl) were processed for hydrolysis of glucuronide and sulphated metabolites using a modified version of Ito *et al*. [47]. Urine samples were acidified with acetic acid (20 µl, 0.58 M) and incubated with 1300 units of β-glucoronidase/sulfatase and 300 ng of internal standard at 37 ^{o}C, 120 rpm for 1.5 h. A liquid-liquid extraction with ethyl acetate was performed twice (400 µl and 300 µl). The two organic layers were pooled and evaporated to dryness under N_2 then stored at -80 ^{o}C for 1-4 days until their reconstitution with 100 µl of 40% methanol immediately before injection. Analysis of urine samples was performed on a HPLC system Hewlett-Packard series 1100 binary pump, coupled to a triple quadrupole mass spectrometer, Micromass Quattro LC (Micromass, Limited), operating in negative electrospray ionization (ES-) mode, equipped with a Zorbax SB-C18 column (2.1 x 50mm, 3.5mm, Agilent). Ionization and fragmentation were optimized for each polyphenol by direct infusion of a standard solution and specific values for collision energy parameters were identified for each polyphenol. Peak for each polyphenol identity was established by the parent and daughter ion pair peak and retention time. Solvents A (water with 0.1% v/v formic acid) and B (acetonitrile with 0.1% v/v formic acid) were run in a 95/5% proportion at a flow rate of 0.2 ml/min with the following gradient:

0–1 min, 5% solvent B; 1–4 min, increase solvent B from 5% to 10%; 4–5 min, increase solvent B from 10% to 90%, 5-5.2 min, decrease solvent B from 90% to 5%, 5.2-15 min isocratic for 9.8 min. Peak areas were plotted against the internal standard response. A good linearity (r^2 0.970–0.990) was observed for all the polyphenols quantified except for luteolin (r^2= 0.922). Samples were run in the same batch and chromatograms were processed automatically by MassLynx Mass Spectrometry Software (MASSLYNX^{TM} version 3.5) using the same processing integrate parameters, peak-to-peak amplitude and peak detection. Intra-assay coefficients of variability were phloretin 7.5%, epicatechin 6%, hesperetin 21.9%, eriodictyol 9.6%, luteolin 9.8%, quercetin 10.8%, daidzein 3.1%, gallic acid 21.4%, vanillic acid 14.4% and enterolactone 5.1%. Final quantities of phenolics compounds were estimated after adjustment by urinary volume. Calibration curves were prepared by spiking HPLC-grade water with 2.5, 5, 12.5, 25, 50, 100, 150, 200 and 250 µl of mixed polyphenols working solution and 100 µl of internal standard working solution, the calibration curve range was 5-500 ng/ml. Spiked HPLC-grade water samples were treated with enzyme and extracted with ethyl acetate as were the urine samples, spiked samples were injected in duplicate at each concentration level. Limits of quantification were established using the spiked samples for calibrations curves; minimum detected values were 5 ng/ml for phloretin, epicatechin, eriodictyol, hesperetin, luteolin, daidzein, gallic acid and vanillic acid and 10 ng/ml for quercetin and enterolactone.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) v.21. Four-day food diary intake data[64] were expressed as weight of intake (g) per day per 10 MJ energy intake, in order to adjust for variability in total food intake between individuals over the 4 days, whereas FFQ data were expressed simply as weight of intake (g) per day. Normality of data distribution was evaluated visually by inspection of histograms and normal Q-Q plots. Non-normally distributed variables were natural log transformed prior to statistical analysis by parametric methods, or analysed by non-parametric methods where log transformation failed to yield a normal distribution. Independent sample t-tests were conducted to compare groups at baseline in order to verify that the polyphenol intakes of each treatment group were similar before the dietary intervention. Where data were normally distributed, one-way analysis of variance with gender as a fixed factor and baseline value as covariate (ANCOVA) was conducted to find differences between groups at endpoint. Where data could not be transformed to a normal distribution, a Mann-Whitney U test was conducted to find differences

between groups at endpoint. Correlation analyses on urinary and dietary polyphenols were conducted by two-tailed Spearman's correlations.

Results

A total of 165 healthy men and women aged 40–70 years were recruited, and 162 completed the CRESSIDA study (64 M, 97 F) (**Figure 1**). Dietary intake of polyphenols was quantified from 322 x 4-DFD (n=161) and from 322 FFQ (n=161) (EPIC-Norfolk FFQ v.6)[61] at baseline and endpoint of the 12-wk intervention, one participant randomised to the DG group did not complete the collection of food diaries therefore was eliminated from the analysis. Urinary excretion of polyphenols was analysed in a subsample (n=91) of the CRESSIDA study, 45 samples from participants in the control group reporting the lowest intakes of F&V, and 46 samples from participants in the intervention group reporting the highest intakes of F&V.

Characteristics of the whole CRESSIDA study population at baseline are shown in **Table 1.** Mean BMI was significantly higher in the control group. Intakes of wholegrain cereals, fruits and vegetables and dietary fibre were higher in the study population at baseline than those reported in a larger, representative UK population sample [11, 56]. As reported previously, at endpoint urinary potassium excretion was 9 mmol/d greater in the DG group indicating higher consumption of fruit and vegetables. Reported wholegrain cereal intake was 81 g/d at endpoint in the DG group (mainly wheat, oats and rice) compared with 32 g/d in the control group, as confirmed by higher plasma alkylresorcinol concentrations, reflecting intakes of whole grains mainly from wheat, barley, and rye [56].

Four-day food diary

Median total polyphenol intake at baseline in the whole study population (with lower and upper limits of IQR) was 1183 mg/d (745, 1613), or 1282 mg/d per 10 MJ energy intake (896, 1838). As shown in **Table 2**, baseline intakes of total polyphenols were significantly higher in the DG group compared to the control group due to greater intakes of total flavonoids, the main contributor being total proanthocyanidins.

At endpoint, total polyphenol intakes per 10 MJ energy intake, adjusted for gender and baseline polyphenol intake, were higher in the DG group than in the control group (**Table 2**). Analysis of intakes of polyphenol classes at endpoint (unadjusted for gender and baseline as non-parametric statistical analysis was necessary) demonstrated that the DG group had higher intakes of total

flavonoids (although also higher in DG at baseline), total lignans, phenolic acids, stilbenes, and "other polyphenols" compared to the control group. For the major flavonoid subclasses, the DG group reported higher intakes of anthocyanidins, proanthocyanidins (although these were also higher at baseline), and isoflavones, but not dihydrochalcones, flavanols, flavones or flavonols. For the major phenolic acids subclasses, the DG group reported higher intakes of hydroxycinnamic acids, but the trend for higher intakes of hydroxybenzoic acids was not statistically significant.

For individual (poly)phenols, there were no differences between groups at baseline, but at endpoint the group following the DG diet reported higher intakes of a number of anthocyanidins including cyanidin, malvidin, peonidin and petunidin ($P<0.05$) compared to the control group. Furthermore, intakes of individual flavanones (naringenin, eriodictyol, and hesperetin, $P<0.05$), a flavone (luteolin, $P<0.05$), and isoflavones (daidzein and genistein, $P<0.01$) were higher in the DG group compared to the control group at endpoint. With regards to lignans, phenolic acids and stilbenes classes, there were higher intakes of secoisolariciresinol ($P<0.05$), matairesinol ($P<0.001$), protocatechuic acid ($P<0.01$), vanillic acid ($P<0.001$), 4-hydroxybenzoic acid ($P<0.001$), syringic acid ($P<0.001$), p-coumaric acid ($P<0.001$) and ferulic acid ($P<0.05$) at endpoint in the DG group compared to the control group. There were no differences between groups in individual flavonols (including kaempferol, quercetin, myricetin and isorhamnetin) nor flavanols (including individual catechins and theaflavins).

The main sources of total polyphenols at endpoint in both groups were tea, coffee & wine (control; 61%, DG; 59%), fruits (control; 10%, DG; 17%) and fruit juices (control; 8%, DG; 4%) (**Figure 2**). Main sources of flavonoids in control and DG groups were tea, coffee & wine (control; 55%, DG; 55%), fruits (control; 14%, DG; 21%) and fruit juices (control; 10%, DG; 5%). Main sources of the flavanols subclass were tea, coffee & wine (control; 64%, DG; 65%), fruits (control; 13%, DG; 19%) and chocolates (control; 11%, DG; 4%). There was an increase in the percentage of polyphenols sourced by fruits, cereal products (breakfast cereal and cereal bar) and nuts & seeds (see **Figure 3** for further details) in the group following the DG diet compared to baseline. There was a decrease in percentage of polyphenols derived from less recommended food options as fruit juices, chocolates and biscuits (**Figure 3**).

Food frequency questionnaire

There were no differences in total flavonoids and flavonoid subclass estimated intakes between groups at baseline. At endpoint the DG group reported higher intakes of total flavonoids, total anthocyanidins,

total flavones, total flavanols, and total proanthocyanidins (**Table 3**). Flavanone and flavonol intakes did not differ between groups at endpoint. Differences between individual polyphenol components revealed higher reported intakes of cyanidin, delphinidin, petunidin and peonidin ($P<0.001$), malvidin and pelargonidin ($P<0.005$), catechin ($P<0.01$), and epicatechin-3-O-gallate, epigallocatechin-3-O-gallate, myricetin and luteolin ($P<0.05$) in the DG group (data not shown) compared to control.

Urinary polyphenol excretion

The ten aglycones quantified in urine were either metabolites of parent glucuronide/sulphated compounds formed in human tissues, or metabolites produced by the gut microbiota, e.g. enterolactone from lignans present in fibre-rich food. At endpoint there was a greater 24 h urinary excretion of phloretin, eriodictyol, hesperetin, luteolin, quercetin, gallic acid, vanillic acid and enterolactone in the DG group compared to the control group (**Table 4**), and a non-significant tendency towards a similar response for daidzein excretion. Daidzein was not detected in 37 participants of the 91 subsample, which could contribute to the lack of significance in the results given that values observed are considerably higher in the intervention group. The only polyphenol that was excreted in similar amounts in both dietary groups was epicatechin.

Discussion

The aim of this secondary analysis of dietary intake data from the CRESSIDA trial was to investigate whether following advice to adhere to UK dietary guidelines increased polyphenol intakes. Baseline polyphenol/flavonoid intakes from 4-DFD and FFQ were in alignment with previous reports in UK populations using 24 h recall[27, 28, 29, 30, 31, 65, 66, 67] or FFQ[15]. The hypothesis was supported by the finding that total estimated polyphenol intakes were approximately 200 mg per 10 MJ energy intake higher at endpoint in the DG group compared to the control group. However, estimates of total polyphenol intakes are only as accurate as the polyphenol composition data, and rely on the sum of the components, which may lead to underestimates if complete composition profile data are unavailable for individual foods. Therefore, total polyphenol intake data should be interpreted in the context of the individual polyphenol intakes. Estimated dietary intakes by 4-DFD showed that the DG group had higher intakes of individual polyphenols/phenolic acids where main food sources were fruits and vegetables (cyanidin, malvidin, peonidin, petunidin, protocatechuic acid, naringenin, eriodictyol, hesperetin and syringic acid), nuts and seeds (secoisolariciresinol and matairesinol) and soy products (daidzein, genistein and other isoflavonoids) compared to the control group. In agreement with the 4-

DFD results, FFQ estimates of total flavonoids, proanthocyanidins and anthocyanidins were higher in the DG group compared to the control group. Ten representative aglycone polyphenols and phenolic acids (from glucuronidated and sulphated metabolites) were measured in 24 h urine samples collected concurrently with 4-DFD as objective biomarkers of (poly)phenol intakes, in order to determine the accuracy of the dietary intake estimates. The ability to discriminate between the dietary group subsamples was consistent with 4-DFD, except for epicatechin, daidzein and quercetin where there were no significant differences in urinary excretion in contrast with higher estimated intakes in the DG group by 4-DFD. Both the 4-DFD and urinary biomarker methods agreed that intakes of phlorizin/phloretin, eriodictyol, hesperidin, luteolin, vanillic acid and lignans/enterolactone were greater in the DG group.

The ability to discriminate between dietary intervention groups supports the utility of 4-DFD and urinary metabolites for assessment of dihydrochalcones, flavanones, flavones, hydroxybenzoic acids and lignan intakes over short-term periods. Differing findings may be due to incomplete phenolic composition data, the well-known inaccuracies of self-reported dietary assessment methodology[68, 69], and the inter-individual variability in absorption and metabolism[8, 70] or incomplete deconjugation of sulphated/glucuronidated metabolites[71] reflected in the urinary biomarkers. Urine polyphenol concentrations may also be the sum product of endogenous metabolism and dietary intakes. For example, gallic acid is a common metabolite of black tea theaflavins and thearubigins[72, 73], therefore its urinary excretion could reflect the consumption of such beverage combined with foods providing gallic acid *per se*. Vanillic acid can be found in high concentrations in foods consumed in small quantities such as herbs; also in moderate concentration in dates, olives and cranberries and in low concentrations in foods more frequently consumed like oats and rice[39]. It is also a common metabolite of anthocyanins[74, 75], and so variability in urinary vanillic acid excretion could reflect varying intakes of both vanillic acid and anthocyanin-rich foods, therefore it is likely that the increased urinary excretion at endpoint mainly represents intake of foods rich in anthocyanins rather than vanillic acid. Vanillic acid is also reported to be present in urine after consumption of black tea[76] and dark chocolate[77]; however, intakes of black tea and dark chocolate were not higher in the DG group at endpoint, and therefore are unlikely to account for the increased urinary excretion and reported intakes in the 4-DFD. Enterolactone is the main colonic metabolite of lignans, which are phytoestrogenic compounds present in high concentrations in vegetables, cereals and grain products, seeds, nuts and berries and other fruits[65, 78]. These urinary excretion data are in agreement with previous epidemiologial studies[79], supplementation studies where known doses of polyphenols were

administrated[44, 80], in RCTs aiming to increase flavonid-rich fruit and vegetables intake[81] and with population under free-living conditions[43]. Polyphenol urinary excretion has shown to be an useful biomarker of fruit and vegetables intakes, capable of detecting even small changes in studies under controlled diets[45, 82, 83].

Following dietary guidelines did lead to increases in specific polyphenols that have been associated with health benefits (e.g. anthocyanins, flavanones, isoflavones, phenolic acids and lignans[84, 85, 86, 87]. This suggests that consuming at least 5 portions F&V per day and >50 % of cereal intake as wholegrain will lead to an enrichment in dietary polyphenol profiles above and beyond the large amounts of polyphenols supplied by beverages. In particular, estimated anthocyanidin intakes were augmented by following dietary guidelines which may confer a reduction in risk of T2D[25], and acute reductions in postprandial glycaemia[88, 89, 90,91]. The dietary intake results reported here are consistent with the theory that greater intakes of specific polyphenols may contribute to the protective effects of a diet rich in fruits and vegetables and wholegrain cereals, alongside greater dietary intakes of nutrients and other non-nutrient bioactives, e.g. potassium, vitamin C, soluble fibre, carotenoids and glucosinolates. However, our results confirm[29, 30, 31] that food groups that are recommended by UK government as part of the Eatwell Guide – fruits and vegetables, wholegrain cereals, beans, pulses, nuts and seeds - contribute a much smaller proportion of daily polyphenol intakes in a UK population compared to commonly consumed beverages, even when that population is following dietary guidelines. Analysis of dietary data showed no group differences in (poly)phenol intakes (by 4-DFD) where main food sources were not targets for UK dietary guidelines such as tea (catechins, theaflavins, proanthocyanidins, quercetin) and wine (stilbenes, proanthocyanidins). However, the sources of these polyphenols may have differed between groups; for example, the DG group reported lower intakes of stilbenes from wine and increased intakes of stilbenes from fruit.

The relative impacts of total and specific (poly)phenol intakes on risk of CVD and type 2 diabetes requires investigation. Clearly there is only limited scope for increasing total polyphenol intake by following dietary guidelines – an approximate increase of 200 mg per day per 10 MJ energy intake. The extent to which this is relevant to cardio-metabolic health is currently unclear due to the lack of robust evidence for the relative impact of different polyphenol subclasses on risk factors for CVD and type 2 diabetes. Although the evidence is currently insufficient, it is plausible to hypothesize that in the future there may be consensus that tea and coffee (poly)phenols[92, 93] may have some of the strongest cardio-metabolic protective effects amongst all dietary phenolics, so that due to the large

amounts of tea and coffee consumed at a population level, the gain to health in consuming at least 5 portions/day of fruits and vegetables and choosing wholegrain sources of starchy carbohydrates is likely to be due to other nutritional factors. Conversely, future advances in nutritional science may one day demonstrate that certain polyphenols specific to fruits, vegetables or wholegrain cereals have particularly potent bioactivity in preventing inflammation, atherosclerosis or insulin resistance, which would bring about a departure from the prevailing approach of considering all plant chemicals that contain a similar chemical structure in the same way. There has been some debate around whether establishing dietary reference intakes (DRI) for polyphenols could be beneficial; with suggested approaches including recommendations for polyphenol-rich F&V (5-a-day)[52], establishing a specific daily dose for a given effect[54] or establishing values to improve health or prevent disease risk in different life stages[53]. Further research is required to provide robust interventional evidence for any refinement to current "5-a-day" guidelines, since the relative health impact of a multitude of other non-nutrient bioactives and the complex array of plant cell wall polysaccharides, resistant starch and oligosaccharides (collectively known as fibre) contained in low-polyphenol plant-based foods is only partially understood. Furthermore, in the light of the fact that NDNS survey data suggest that the UK population are not meeting current recommendations for F&V then it would be futile, and possibly counter-productive, to add further complexity to existing public health dietary advice.

The validation of adequate biomarkers of dietary intake, of exposure to dietary components and of compliance to dietary interventions has been a focus of investigation for many years[94] and the identification of polyphenol intake biomarkers is no exception[83, 95]. Assessment of compliance in dietary intervention studies with fruits and vegetables has been done by validated biomarkers[96] such as vitamin C, carotenoids and potassium, however polyphenol excretion in urine may be used to assess flavonoid-rich dietary interventions[81] or specific fruit and vegetable intakes, for example phloretin for apple intake and naringenin and hesperetin for citrus fruit[95, 97]. Given the importance of accurate assessment of polyphenol intake in order to link it with beneficial effects on health[98], the ability to detect the amount consumed represents a challenge in epidemiological and clinical studies.

The bespoke food composition table developed for the 4-DFD polyphenol analysis in the present study included the estimation of 52 individual compounds and contained 1141 foods representative of an average UK diet as well as some of the most commonly eaten food from non-traditional UK cuisine as Turkish, Indian, Italian, Chinese, Japanese, and others. This food composition table could be used as a basis for future studies analysing diet patterns in the UK population, comparing

polyphenols intake and/or linking intake with health benefits, although it would require a significant staff cost commitment to maintain and update with new recipes and new versions of Phenol Explorer over time. Although an onerous process, the creation of a bespoke food composition table for polyphenol analysis in a specific population seems to be the most effective way to obtain an accurate estimation of polyphenol intake. Although the FFQ is a valid and reliable dietary assessment tool for estimation of habitual intake in populations, it has limitations in the way that it can collect information, since it is based on uniform estimated portion sizes and is semi-quantitative. Dietary intake of total flavonoid intake, six flavonoid subclasses and 32 individual flavonoids (aglycones) were estimated by FFQ (EPIC-Norfolk) using methodology previously applied in large cohort studies[15, 17, 23, 25, 26, 99]. The EPIC-Norfolk FFQ, although validated for whole foods intake[100], has not been validated for flavonoid intake. Methodological barriers of this approach in regard to flavonoid estimation are particularly limiting in smaller study cohorts: some foods are grouped incongruously with regards to their flavonoid composition such as "strawberries, raspberries and kiwi", or "peaches, plums and apricots" and "wine" (no separation of red, white and rosé). Some important flavonoid sources are missing such as blueberries, soy beverages, and lemon, among others. The inadequacy of this method could lead to under- or overestimation of flavonoid intakes. Studies have used food diaries for estimation of flavanol intake in European populations[29], isoflavone and lignan intakes[66] and 20 subclasses of polyphenols[31] in a UK population, each one creating their own food composition table for polyphenol analysis, however they have not included objective biomarkers for corroborating agreement between methods. More specialised questionnaires for intake estimation have been developed for individual compounds like quercetin and naringenin [101], flavonoid subclasses such as flavonols and flavones in a Chinese population[102], complete flavonoid class in Australian population[34] and Flemish population[103]. In summary, although the FFQ results reported here were in broad agreement with the 4-DFD regarding the discernment of differences in total flavonoid intakes in a dietary intervention study, future research in this area could include the development of a specific FFQ, validated in a UK population, for estimation of phenolic intakes including all classes and main subclasses as were estimated by 4-DFD in this study.

Limitations in the present study include the hydrolysis of urinary polyphenols by glucoronidase/sulphatase enzymes prior to analysis, which could compromise the stability of polyphenols that are to be quantified [104, 105]. Glucoronidase/sulphatase enzymes may fail to completely hydrolyse all sulphated and methylated-sulphated metabolites, which may have been compounded by the addition of boric acid as a preservative to prevent yeast growth, and therefore urinary excretion of

the corresponding aglycone could be underestimated[71]. Furthermore, our approach required preselection of polyphenols to be analysed which means that many other polyphenols present in 24 h urine that may have also functioned as biomarkers of intake were not detected and quantified. Although reported anthocyanidin intakes were greater in the DG group, we did not attempt to analyse anthocyanins in urine as they have low recovery as parent compounds and only weak correlations with dose ingested, necessitating the use of stable isotopes to accurately measure the excretion of anthocyanin metabolites[44]. The 4-DFD proved to be an accurate approach for estimate of short-term polyphenol intake, however, serious consideration must be made of the potential researcher burden and cost if using these methods in larger scale studies, particularly where a simple indicator of compliance to dietary advice is required.

Strengths of our study include the fact that the data collected in this study enabled a comparison of two dietary assessment methods with objective biomarkers of (poly)phenol dietary intake collected concurrently towards the end of the dietary intervention period. To date, this 3-way comparison has only been reported previously in a cross-sectional[106] study using a crude estimate of total urinary polyphenol excretion by the Folin-Ciocalteu assay. To the best of our knowledge this is the first study to use the 3 way comparison on data obtained from an RCT allowing comparison of change from baseline for individuals advised to consume a diet consistent with dietary guidelines.

In conclusion, participants following advice to adhere to UK dietary guidelines consumed a greater amount of total polyphenols than a control group consuming a representative UK diet. In particular, intakes of individual polyphenols that are mainly sourced from fruits and vegetables, nuts, seeds and soy products were increased in the DG group. The results of this study advance the field of polyphenol research as they demonstrate that a diet consistent with dietary guidelines is also moderately richer in polyphenols compared to a typical UK dietary pattern, despite the relatively high baseline intakes derived from commonly consumed beverages such as tea and coffee. In addition to increased intakes of dietary fibre and certain micronutrients, replacement of saturated fatty acids with unsaturated fatty acids, and lower salt and free sugars, following dietary guidelines will also increase polyphenol intakes which may contribute to the overall reduction in risk factors for cardiometabolic diseases.

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Conflict of Interest

W.L.H. has current collaboration with Lucozade Ribena Suntory and DIANA Food SAS. T.A.B.S., D.P.R., J.D and M.L.C.A. reported no conflicts of interest.

Authorship

T.A.B.S. was principal investigator of the CRESSIDA study. T.A.B.S. and W.L.H. devised the CRESSIDA study, D.P.R. and J.D. recruited subjects into the study and supported the dietary intervention in the CRESSIDA study. M.L.C.A. and W.L.H. conceived the idea for secondary analysis of polyphenols intake data, analysed data, performed statistical analysis. M.L.C.A. wrote drafts of the manuscripts, which were edited by W.L.H. The manuscript was read, commented on, and approved by all authors.

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Figure legends

Figure 1 Flow of participants through the CRESSIDA study

Figure 2 Main polyphenol food sources in control and dietary guidelines groups, at endpoint, of the CRESSIDA study as estimated by four-day food diary

Figure 3 Percentage changes from baseline in main food group sources of polyphenols in dietary guidelines group as estimated by four-day food diary

Table 1 Baseline characteristics of the CRESSIDA study population by randomised group

Characteristic	**Control** (n=82)		**Dietary Guidelines** (n=79)		**Difference between groups** *(P* value)*
Gender (n)					
Female	50		47		
Male	32		32		
	Mean	SD	Mean	SD	
Age (years)	52	8.0	53	8.0	0.717
BMI (kg/m^2)	26.8	3.9	25.4	3.7	0.019
Waist circumference (cm)					
Female/male	91.9/98.2	10.0/12.2	87.1/97.3	12.2/9.3	0.093
SBP (mmHg)	122.0	11.5	121.6	14.3	0.848
DBP (mmHg)	73.9	7.1	73.8	8.0	0.930
Glucose (mmol/L)	5.0	0.4	5.3	0.5	0.990
Total cholesterol (mmol/L)	5.3	0.9	5.4	1.1	0.983
TC:HDL cholesterol ratio	3.6	1.0	3.5	1.0	0.262

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
*Statistical comparisons between groups at baseline by independent T-test or independent samples Mann-Whitney U-test.

Table 2 Daily intake of polyphenols estimated by four-day food diary and adjusted for energy intake following dietary guidelines and control diets.

Polyphenols (mg/d/10 MJ) Classes and *subclasses*	Baseline (n=161)		Endpoint (n=161)				Differences between groups at endpoint ($P^{‡}$)
			Control (n=82)		Dietary Guidelines (n=79)		
Total polyphenols*	1202[†]	(1093, 1323)	1084	(980, 1197)	1279	(1158, 1412)	0.023[§]
Flavonoids	840[†]	(536, 1263)	802	(456, 1109)	882	(610, 1401)	0.014
Anthocyanidins	55	(14, 130)	30	(14, 108)	76	(25, 144)	0.032
Dihydrochalcones	1.6	(0.0, 3.8)	2	(0, 4)	2	(1, 6)	0.297
Flavanols	349	(114, 526)	311	(104, 498)	394	(128, 665)	0.159
Proanthocyanidins	231[†]	(117, 339)	195	(115, 324)	249	(169, 381)	0.020
Flavanones	31	(4, 64)	24	(2, 58)	33	(8, 84)	0.096
Flavones	6	(3, 12)	5	(1, 12)	5	(2, 12)	0.603
Flavonols	80	(51, 112)	80	(50, 105)	83	(58, 127)	0.125
Isoflavones	0.3	(0.1, 9.9)	0.1	(0.1, 0.4)	0.5	(0.1, 65.0)	0.002
Lignans	0.5	(0.2, 5.0)	0.3	(0.1, 0.4)	0.5	(0.2, 6.0)	<0.001
Phenolic acids	289	(185, 569)	221	(132, 493)	344	(209, 522)	0.012
Hydroxybenzoic acids	90	(35, 143)	75	(32, 125)	100	(55, 170)	0.067
Hydroxycinnamic acids	149	(88, 450)	119	(59, 378)	172	(99, 444)	0.018
Stilbenes	0.09	(0.02, 0.71)	0.09	(0.02, 0.94)	0.26	(0.07, 1.25)	0.042
Other polyphenols	21	(11, 41)	13	(6, 30)	37	(20, 58)	<0.001

All values are medians (with lower and upper limits of IQR), except where * denotes values are geometric means (95% CI), adjusted for baseline and gender at endpoint.
[†]Statistically significant differences between groups at baseline by independent T-test (total polyphenols) or independent samples Mann-Whitney U-test (all other comparisons); intakes were higher in the DG group than the control group, $P<0.05$.
[‡]Statistical comparisons between groups at endpoint by Mann-Whitney U-test, except where [§] denotes statistical comparisons between groups at endpoint adjusted for baseline and gender by ANCOVA.

Table 3 Median daily intake of flavonoids estimated by food frequency questionnaire in dietary guidelines and control groups

Flavonoids (mg/d) Class and *subclasses*	Baseline (n=161)		Endpoint (n=161)				Differences between groups at endpoint (*P**)
			Control (82)		Dietary Guidelines (79)		
Total flavonoids	661	(417, 867)	539	(350, 862)	715	(571, 906)	0.005
Anthocyanidins	19	(10, 35)	16	(9, 31)	32	(19, 50)	<0.001
Flavones	2.4	(1.6, 3.5)	2.7	(1.5, 3.7)	3.2	(2.0, 4.4)	0.013
Flavonols	35	(23, 47)	39	(21, 54)	39	(31, 50)	0.199
Flavanols	90	(40, 143)	85	(35, 146)	97	(80, 143)	0.048
Flavanones	23	(8, 42)	25	(10, 43)	27	(8, 49)	0.352
Proanthocyanidins	265	(184, 379)	232	(184, 371)	290	(229, 385)	0.021

Values are medians (lower and upper limits of the IQR). There were no significant differences between groups at baseline.
* Statistical comparisons between groups at endpoint by Mann-Whitney U-test.

Table 4 Comparison of urinary phenolic excretion method and polyphenol intake estimated by 4-day food diary in their ability to discriminate between subsample populations either adhering to dietary guidelines or a control diet.

Polyphenols	Urinary excretion† (µmol/d)					Dietary intake (mg/d/10 MJ)				
	Control (n=46)		Dietary Guidelines (n=45)		Difference between groups (*P*)	Control (n=46)		Dietary Guidelines (n=45)		Difference between groups (*P*)
Phloretin‡	0.09	(0.01, 0.28)	0.40*	(0.18, 0.97)	<0.001	1.2	(0.0, 3.5)	3.1*	(1.1, 5.9)	0.006
Epicatechin	0.45	(0.24, 0.60)	0.44	(0.21, 0.70)	0.943	30	(15, 50)	40*	(29, 67)	0.013
Eriodictyol	0.25	(0.09, 0.43)	0.51*	(0.20, 0.86)	0.011	0.00	(0.00, 0.02)	0.02*	(0.01, 0.06)	<0.001
Hesperetin	0.20	(0.00, 2.03)	1.38*	(0.09, 3.51)	0.010	8	(1, 23)	17*	(4, 35)	0.019
Luteolin	1.8	(0.9, 2.9)	2.7*	(1.5, 3.7)	0.017	0.5	(0.3, -8)	1.5*	(0.9, 3.3)	<0.001
Quercetin	4.7	(1.5, 7.4)	6.6	(2.4, 12.8)	0.105	50	(27, 66)	59*	(41, 85)	0.028
Daidzein	0.02	(0.00, 0.40)	0.11	(0.00, 0.80)	0.074	0.04	(0.04, 0.10)	3.5*	(0.02, 21.2)	0.006
Gallic acid	0.7	(0.2, 2.0)	1.4	(0.5, 3.6)	0.053	62	(18, 107)	90	(23, 153)	0.134
Vanillic acid	1.4	(0.2, 2.6)	3.0*	(0.9, 5.9)	0.023	0.2	(0.1, 0.2)	0.4*	(0.2, 0.6)	<0.001
Lignan/ Enterolactone§	5.7	(2.1, 10.6)	10.1*	(3.8, 22.6)	0.010	0.2	(0.1, 0.4)	0.6*	(0.3, 6.1)	<0.001

Excretion of polyphenols in 24 h urine and dietary intake of the direct dietary precursor estimated by 4-DFD at endpoint in a subsample of the CRESSIDA study population selected for the lowest (control group) and highest (dietary guidelines group) fruit and vegetables intake using self-reported data from food frequency questionnaires (n=91).

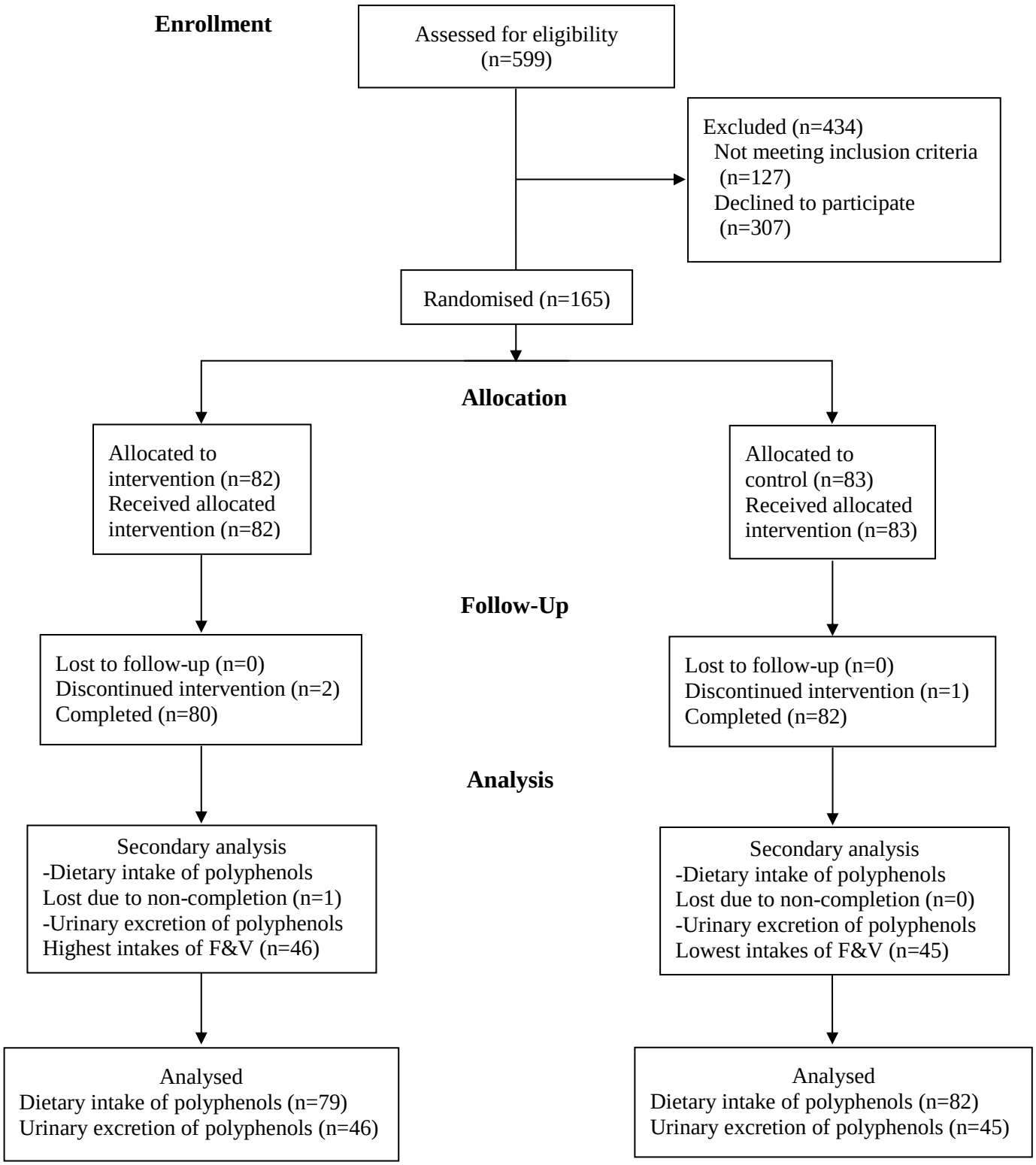
All values are median (lower and upper limits of IQR). All between group comparisons were carried out by independent samples Mann-Whitney U Test.

† Values adjusted for 24 h urine volume.

‡ Sum of phloretin and phlorizin

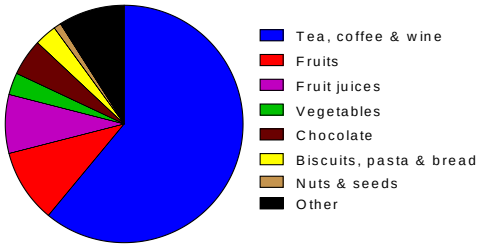
§ Intake of lignans was used as direct dietary precursor of enterolactone.

*Statistically significant differences between groups at endpoint, $P<0.05$.

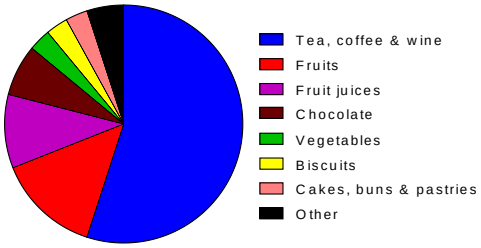

Enrollment
Assessed for eligibility (n=599)
Excluded (n=434)
Not meeting inclusion criteria (n=127)
Declined to participate (n=307)
Randomised (n=165)
Allocation
Allocated to intervention (n=82)
Received allocated intervention (n=82)
Allocated to control (n=83)
Received allocated intervention (n=83)
Follow-Up
Lost to follow-up (n=0)
Discontinued intervention (n=2)
Completed (n=80)
Lost to follow-up (n=0)
Discontinued intervention (n=1)
Completed (n=82)
Analysis
Secondary analysis
-Dietary intake of polyphenols
Lost due to non-completion (n=1)
-Urinary excretion of polyphenols
Highest intakes of F&V (n=46)
Secondary analysis
-Dietary intake of polyphenols
Lost due to non-completion (n=0)
-Urinary excretion of polyphenols
Lowest intakes of F&V (n=45)
Analysed
Dietary intake of polyphenols (n=79)
Urinary excretion of polyphenols (n=46)
Analysed
Dietary intake of polyphenols (n=82)
Urinary excretion of polyphenols (n=45)

Control diet

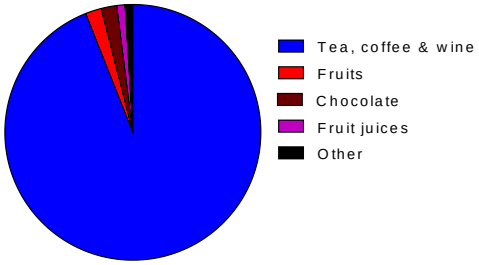
Total polyphenols



Flavonoids



Flavanols

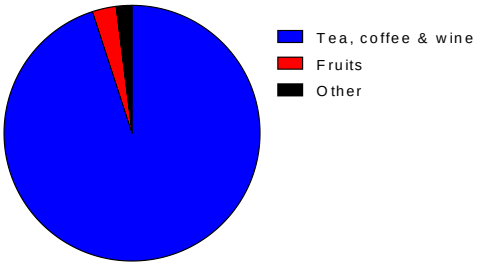


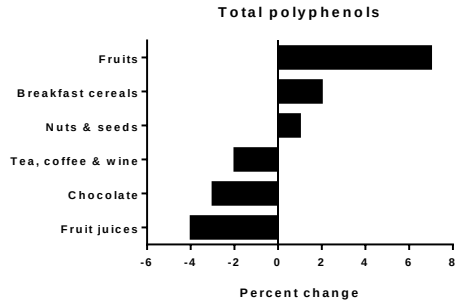
Dietary guideline diet

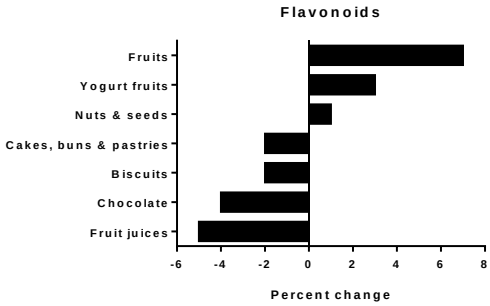
Total polyphenols

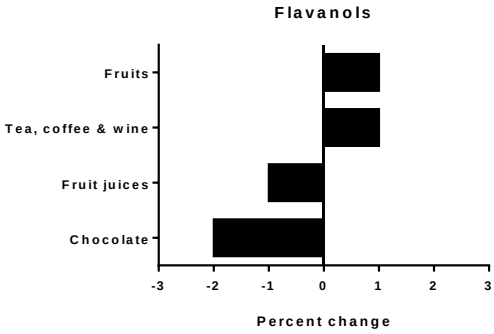
Flavonoids

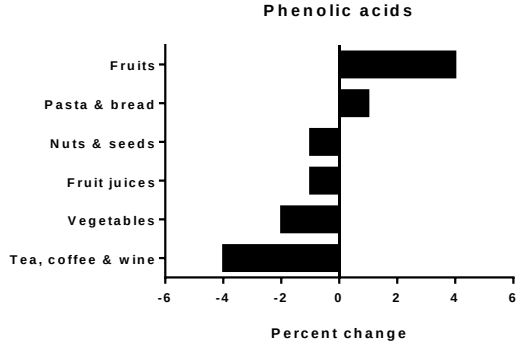
Flavanols

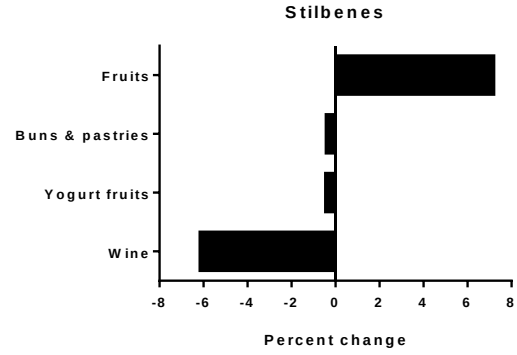


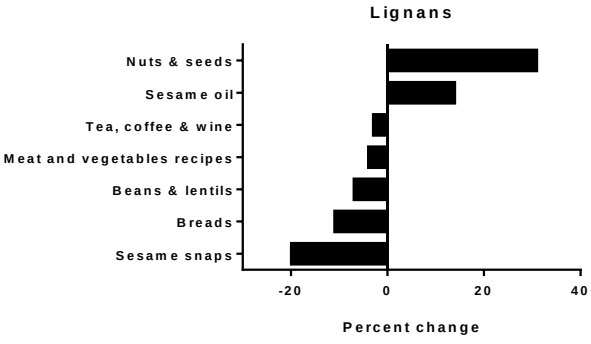

Total polyphenols
Fruits
Breakfast cereals
Nuts & seeds
Tea, coffee & wine
Chocolate
Fruit juices
-6 -4 -2 0 2 4 6 8
Percent change


Flavonoids
Fruits
Yogurt fruits
Nuts & seeds
Cakes, buns & pastries
Biscuits
Chocolate
Fruit juices
-6 -4 -2 0 2 4 6 8
Percent change


Flavanols
Fruits
Tea, coffee & wine
Fruit juices
Chocolate
-3 -2 -1 0 1 2 3
Percent change


Phenolic acids
Fruits
Pasta & bread
Nuts & seeds
Fruit juices
Vegetables
Tea, coffee & wine
-6 -4 -2 0 2 4 6
Percent change


Stilbenes
Fruits
Buns & pastries
Yogurt fruits
Wine
-8 -6 -4 -2 0 2 4 6 8
Percent change


Lignans
Nuts & seeds
Sesame oil
Tea, coffee & wine
Meat and vegetables recipes
Beans & lentils
Breads
Sesame snaps
-20 0 20 40
Percent change