#### Supplementary material:

#### Kinetics of absorption

Studies investigating CO need to consider the kinetics of blood βHB concentrations following MCFA (or CO) intake to maintain optimal ketone body production in AD patients, in addition to accounting for effective yet safe doses. For example, Axona®, containing the MCFA caprylic acid (C8H16O2), retailed as a medical food, has been reported to improve cognitive performance and elevate serum βHB two hours post administration (Henderson et al., 2009). As per the prescription information available on the Axona® website (http://www.about-axona.com/), the intake of Axona® has been prescribed once daily following a substantial meal. However, further studies are required to investigate the kinetics of elevated serum βHB concentrations several hours following Axona® administration, and whether the addition of longer MCFA (such as capric acid and lauric acid) to caprylic acid can potentially extend the duration of elevated serum βHB concentrations, in turn extending the duration of its beneficial effects per dose. Additionally, investigating the intake of multiple daily doses of MCFA may also serve as an alternative strategy to maintain a steady yet safe source of ketone bodies for the brain, serving as an alternative source of energy in AD as well as other glucose hypometabolism disorders (Vandenberghe et al., 2017). However, a relatively recent study on an Experimental Autoimmune Encephalomyelitis mouse model showed that lauric acid enhanced differentiation and proliferation of immune activating proinflammatory cells (T helper 1 and/or 17) and impaired their intestinal sequestration via a proinflammatory (p38-MAPK) pathway. In contrast, dietary short chain fatty acids (SCFA; C3, C4, C6) expanded gut T regulatory cells by suppression of proinflammatory pathways (JNK1 and p38) therefore ameliorating the proinflammatory signals in the gut (Haghikia et al., 2015). SCFA are produced by the gut microbiota from dietary fibre, primarily comprising plant cell wall polysaccharides, oligosaccharides and resistant starches. Interestingly, studies have reported that the average western diet contains 20-25g fibre/day while a diet high in fruits and vegetables could contain up to 60g fibre/day, highlighting the importance of accompanying MCT intake with high fruit and vegetable intake.

#### Clinical studies of ketone supplement dosage and effects on CMR

A study conducted on mild to moderate AD patients found that 30g/d MCT supplementation for one month increased brain ketone consumption by 2-fold, without affecting glucose utilization (Croteau et al., 2018). Further, a study assessing the impact of diet-induced moderate ketosis on CMRGlu and CMRAcAc in healthy adults following a four-day high fat KD (4.5:1; lipid: protein plus carbohydrates), reported an 8-fold increase in plasma ketones and a 24% decrease in plasma glucose equating to a 6-fold increase in CMRAcAc and a 20% decrease in CMRGlu respectively. This boost in CMRAcAc represented 17% of the whole brain energy requirements in healthy adults with a 2-fold difference across brain regions (12-24%) whereas the combined CMR of AcAc and βHB was estimated to represent about 33% of the brain’s energy requirements (Courchesne-Loyer et al., 2017). Given the potential of a KD, potent ketone fuels such as MCT from coconut oil need to be investigated such that the availability of the specific fatty acids in CO/MCT can be optimized.

#### Conflicting information concerning the saturated fats in CO

A presidential advisory issued by the American Heart Association (AHA) on dietary fats and CVD, concluded that lowering saturated fat intake and replacing it with unsaturated fat, would decrease the incidence of CVD (Sacks et al., 2017). This advice also warned against the dietary intake of CO. The core evidence for this conclusion was primarily based on observations from four clinical trials (Dayton et al., 1969; Leren, 1970; Turpeinen et al., 1979) that compared high intake of saturated fat with high intake of polyunsaturated fat. However, the literature cited was primarily based on studies that employed saturated fats predominantly comprising animal fats (palmitate and stearate, not laurate/myristate). Moreover, the study (Keys et al., 1957) that involved CO, employed a hydrogenated variety of CO (likely to have high trans-fat content (Hilditch and Vidyarthi, 1929)) instead of VCO or natural CO. Furthermore, the different properties (digestion and metabolism) of fatty acids based on carbon chain length (Bragdon and Karmen, 1960; McCarty and DiNicolantonio, 2016), have until recently, rarely been considered. For example, a recent systematic review and meta-analysis on the comparison of the effects of saturated MCFA (6-12 carbon atoms) versus saturated LCFA on lipid profiles showed that MCFA significantly increased plasma HDL-C as well as plasma concentrations of apolipoprotein A-1, the major protein component of HDL particles, compared to LCFA (Panth et al., 2018). This review underscores the importance of considering the effect of the saturated fatty acid chain length on lipid profiles and CVD risk and discusses points which may address concerns raised by the AHA. Needless to say, caloric intake always needs to be considered; if the caloric intake exceeds daily requirements, MCFA will tend to be stored in adipose tissue (Hill et al., 1990). It is also important to note that the beneficial effects of MCFA are modulated by the overall dietary pattern, as this influences MCFA transport to the liver via the portal vein (Swift et al., 1990).

**Supplementary table 1. Evidence from clinical trials on the effect of coconut oil on blood lipids and lipoprotein profiles**

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| Reference  (Country) | Subjects | Study design and length | Intervention | Observations (Mean ± standard deviation, mmol/L unless otherwise stated) | Limitations |
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| Fisher et al, 1983 (USA) (Fisher et al., 1983) | 9 healthy men  18-37 years old healthy weight normo-lipidemic | Non-randomized, cross-over  64 days (9-day oil then 9-day oil + cholesterol, 1-month wash out, 9-day alternate oil then 9-day alternate oil + cholesterol). | Isocaloric diets providing 15%E protein, 54%E carbohydrate and 31%E fat.  Fat sources: corn oil (corn), corn oil + 1g/day cholesterol (corn+), coconut oil (CO), coconut oil + 1g/day cholesterol (CO+). | TC: CO (4.29±0.70) = CO+ (4.65±0.75) > corn (2.95±0.36) = corn+ (3.05±0.28)  LDL-C+IDL-C: CO (2.72±0.65) = CO+ (3.00±0.72) > corn (1.76±0.41) = corn+ (1.78±0.44)  VLDL-C: CO (0.52±0.23) = CO+ (0.67±0.26) > corn (0.34±0.18) = corn+ (0.39±0.18)  HDL-C: CO (1.06±0.18) = CO+ (0.98±0.18) > corn (0.88±0.16) = corn+ (0.88±0.13)  TG: CO (0.89±0.49) = CO+ (1.12±0.25) > corn (0.67±0.19) = corn+ (0.55±0.17)  ApoE (mg/dL): CO (32.0±6.2) = CO+ (32.2±8.5) > corn (24.1±2.7) = corn+ (24.2±3.8); the coconut oil diet shifted ApoE towards lipoproteins of lower density (VLDL, IDL, and LDL) compared with the corn oil diet. | No randomization  No power calculation Small sample size Only men recruited  Not defined if coconut oil was refined or virgin. |
| Mendis and Kumarasundaram, 1990  (Sri Lanka) (Mendis and Kumarasundaram, 1990) | 25 healthy men  20-26 years old | Randomized cross-over  19 weeks (8-week feeding, 3-week wash out, 8-week feeding) | Consumption of 2 high fat meals (lunch and dinner) containing either coconut fat or soya-bean oil and a low-fat high-carbohydrate breakfast. | TC: Coconut (4.61±039) > Soya-bean (3.68±042)  LDL-C: Coconut (2.84±0.37) = Soya-bean (2.27±0.36)  HDL-C: Coconut (1.14±0.27) = Soya-bean (0.94±0.26)  TG: Coconut (1.45±0.41) = Soya-bean (1.06±0.42) | Only men recruited |
| Heber et al, 1992 (USA) (Heber et al., 1992) | 9 healthy males  22-43 years old | Randomized crossover  13 weeks (2-week washout, 3x3-week diet) | Substitution of 50% of total fat and 17.5% of total energy with either (P) palm oil, (CO) coconut oil or (HS) hydrogenated soybean oil. | TC (change): CO significant increase; P and HS not significant  LDL-C (change): CO significant increase; P and HS not significant  HDL-C (change): P significant increase; CO and HS not significant  TG (change): CO, P and HS not significant  ApoAI (change): CO, P and HS not significant  ApoB (change): CO, P and HS not significant | Small sample size  Does not compare diets |
| Cox et al, 1995 (New Zealand) (Cox et al., 1995) | 28 subjects (13 men, 15 women), 29-67 years old  5.5-7.9 mmol/L TC  < 3 mmol/L TG | Randomized, cross-over, no wash out  24 weeks (6-week run in + 3x6-week diet) | Diets providing 17%E protein, 47%E carbohydrate, 36%E fat and cholesterol matched (300-350mg/day). Fat sources: coconut oil (CO) or butter (B), providing 20%E as SFA, or safflower oil (SA), providing 10%E PUFA and 10%E SFA. | TC: B (6.8±0.9) > CO (6.4±0.8) > SA (6.1 ± 0.8)  LDL-C: B (4.5±0.8) > CO (4.2±0.8) > SA (3.9±0.7)  VLDL-C: B (0.65±0.65) = CO (0.54±0.51); B > SA (0.53±0.54); CO = SA  HDL-C: B (1.4±0.4) = CO (1.5±0.4) = SA (1.4±0.3)  ApoAI (mg/L): B (141±23) = CO (157±17) > SA (132±22)  ApoB (mg/dL): B (86 ± 20) = CO (91±32) > SA (77±19)  TG: B (2.0±1.3) > CO (1.8±1.0) = SA (1.7±1.0) | Unbalanced male and female ratios  No wash out |
| Cox et al, 1998  (New Zealand) (Cox et al., 1998) | 37 healthy pacific island Polynesians (24 men and 17 women)  19-72 years old  4.2-7.5 mmol/L TC < 3 mmol/L TG | Sequential, cross over, no wash out  24 weeks (6-week run in + 3x6-week diet) | Diet providing 17%E protein, 47%E carbohydrate, 36%E fat and cholesterol matched (250±300 mg/d).  Fat sources: (B) Butter, 39g butter + palmitic acid rich (~17g palmitic acid); (CO) Coconut oil, 39g coconut oil (~17g lauric acid); (SA) Safflower, 24g safflower oil (~17g linoleic acid) | TC: B (5.61±0.96) = CO (5.47±0.91) > SA (5.10±0.93)  VLDL-C: B (0.34±0.18) = CO (0.41±0.36) = SA (0.45±0.45)  LDL-C: B (4.08±0.89) > CO (3.79±0.75) > SA (3.50±0.84)  HDL-C: B (1.16±0.24) = CO (1.21±0.27) > SA (1.06±0.21)  ApoAI (g/L): B (1.23±0.18) = CO (1.33±0.28) > SA (1.15±0.14)  ApoAII (g/L): B (0.34±0.08) = CO (0.35±0.08) = SA (0.35±0.08)  ApoB (g/L): B (1.00±0.22) > CO (0.87±0.38) = SA (0.76±0.18)  TG: B (1.86±0.89) = CO (1.61±0.93) = SA (1.77±.25) | No randomization  No wash out  Unblinded |
| Assuncao et al, 2009 (Brazil) (Assuncao et al., 2009) | 40 women  20–40 years old  >88cm waist circumfe-rence | Randomized,  double-blind, clinical trial  12 weeks | S: 30 mL of soy bean oil  CO: 30mL of coconut oil  Both combined with a balanced hypocaloric diet and a 50min daily walk. | TC (change): S significant increase; CO not significant  LDL-C (change): S significant increase; CO not significant  HDL-C (change): S significant decrease; CO not significant  LDL-C/HDL-C (change): S significant increase; CO not significant  TG (change): S and CO not significant | No power calculation  Small sample size  Only women  Does not compare diets |
| Voon et al, 2011  (Malaysia) (Voon et al., 2011) | 45 apparently healthy subjects | Crossover, 3 x 3 Latin-square, no wash out  18 weeks (3-week standardization, 3x5-week intervention) | Diet containing 30%E fat, 1/3 from either palmitic acid (16:0) rich palm olein (PO), lauric and myristic acid (12:0+14:0) rich coconut oil (CO) or oleic acid (18:1) rich virgin olive oil (VOO), 20%E protein and 50% carbohydrate. | TC: VOO (4.65±0.71) < CO (4.95±0.69); PO (4.81±0.74) = VOO; PO = CO  LDL-C: VOO (3.06±0.64) < CO (3.30±0.75); PO (3.20±0.71) = VOO; PO = CO  HDL-C: VOO (1.28±0.23) < CO (1.37±0.30); PO (1.31±0.26) = VOO; PO = CO  TG: PO (0.85±0.31) = VOO (0.84±0.37) = CO (0.90±0.39) | No wash out |
| Cardoso et al, 2015  (Brazil) (Cardoso et al., 2015) | 116 (63.2% males)  62.4 ± 7.7 years old  100% hypertense  94.5% dyslipidemic | Non-randomized clinical trial  6 months | **Stage 1**: 3 months intensive nutritional treatment.  **Stage 2:** 3 months either on the standard diet (SD, n=22) or on the standard diet + 13mL/day extra virgin coconut oil (VCO, n=92). | TC (change): VCO (0.15±0.92) = SD (0.29±0.82)  LDL-C (change): VCO (0.10±0.81) = SD (0.07±0.85)  HDL-C (change): VCO (0.08±0.19, p<0.01) > SD (-0.03±0.22)  TG (change): VCO (-0.02±0.80) = SD (0.26±0.82)  ApoA (mg/dL, change): VCO (4.7±12.7, p<0.01) = SD (-3.9 ±2.7, p=0.20)  ApoB (mg/dL, change): VCO (6.4±17.6, p<0.01) = SD (7.4±18.1, p=0.07) | No randomization  Unequal numbers in treatment (VCO) vs control (SD).  Subjects were on lipid-lowering and/or anti-hypertensive drugs. |
| Vijayakumar et al, 2016  (India) (Vijayakumar et al., 2016) | 200 males and females on standard medical care with stable CAD and controlled diabetes and lipid levels. | Randomized, single blinded, clinical trial  2 years | Subjects were supplied with either coconut oil (CO) or sunflower oil (SO) as cooking media to account for 15% of their daily energy intake. | TC (change): CO and SO not significant  LDL-C (change): CO and SO not significant  VLDL-C (change): CO and SO not significant  HDL-C (change): CO and SO not significant  TG (change): CO and SO not significant | Subjects were on statins. |
| Khaw et al, 2018  (United Kingdom) (Khaw et al., 2018) | 91 healthy subjects (2/3 women)  50–75 years | Randomized, unblinded, parallel  4weeks | Subjects consumed 50g/daily of either (VCO) organic extra virgin coconut oil, (EVO) organic unfiltered extra virgin olive oil and (B) organic unsalted butter. | LDL-C (change): B (0.33±0.48) > VCO (−0.09±0.49) = EVO (−0.06±0.39)  HDL (change): VCO (0.28±0.29) > B (0.09±0.27) = EVO (0.10±0.15)  TG (change): VCO (0.07±0.58) = B (−0.001±0.36) = EVO (−0.03±0.27)  TC/HDL-C (change): B (0.10±0.41) > VCO (−0.26±0.36) = EVO (−0.13±0.32)  non HDL-C (change): B (0.33±0.51) > VCO (−0.06±0.44) = EVO (−0.07±0.42) | Short  Unblinded  13% of subjects reported less than 75% compliance. |

= represents no significant difference between interventions, > represents significantly higher values for the intervention on the left of the sign and < represents significantly lower values for the intervention on the left of the sign. ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; ApoE, apolipoprotein E; B, butter; BF, beef fat; CAD, coronary artery disease; change, increase or decrease from baseline values to post-intervention values; CO, coconut oil; %E, percentage energy; EVO, extra virgin olive oil; HDL-C, high density lipoprotein cholesterol; HS, hydrogenated soybean oil; IDL-C, intermediary density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; P, palm oil; PO, palm olein; PUFA, polyunsaturated fatty acids; S, soy bean oil; SA, Safflower; SD, standard diet; SFA, saturated fatty acids; SO, sunflower oil; TC, total cholesterol; TG, triglycerides; VCO, extra virgin coconut oil; VLDL-C, very low density lipoprotein cholesterol; VOO, virgin olive oil.

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