Integrative Medicine in Stroke

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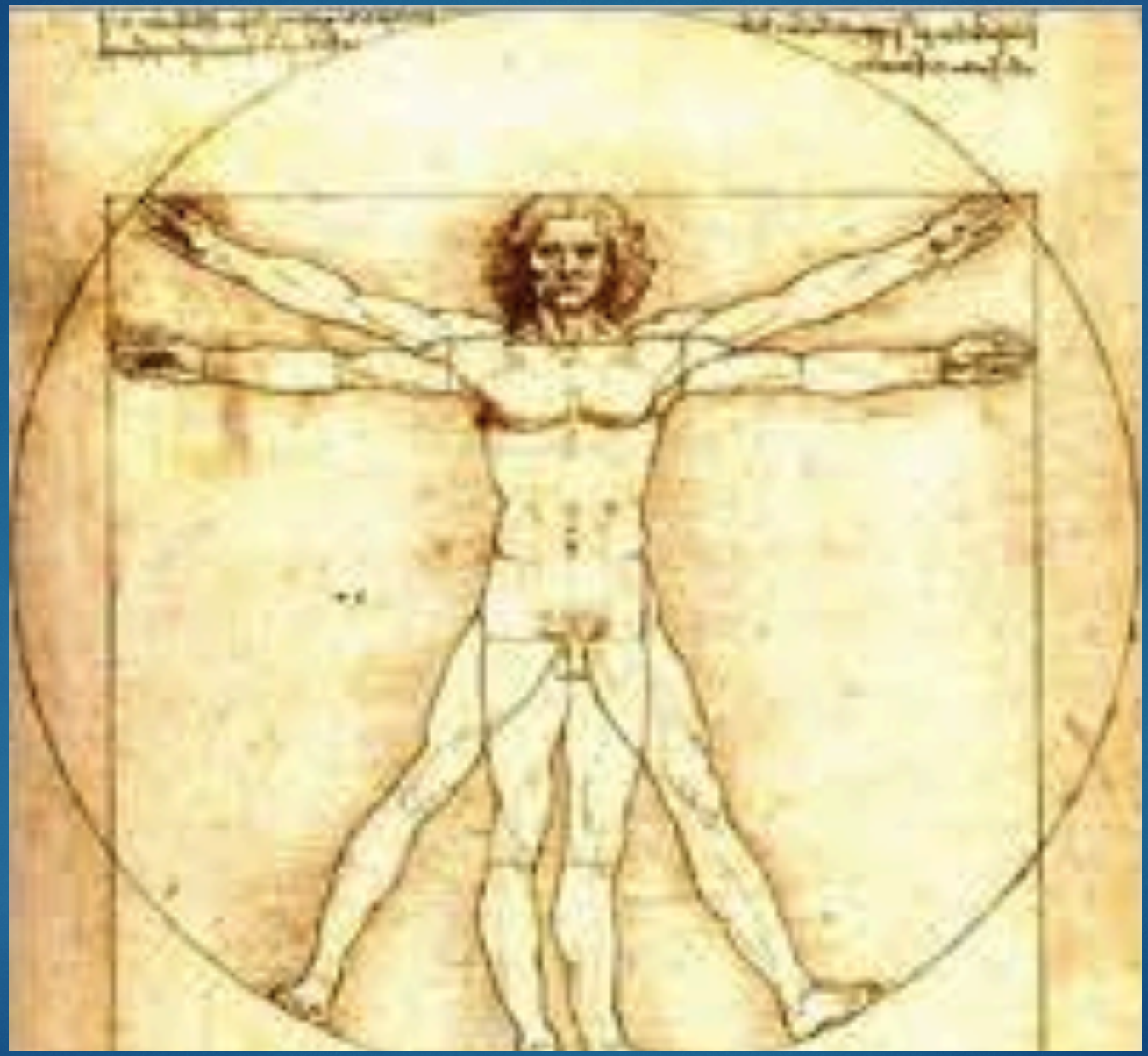
Objectives

- Discuss role of dietary modification in reducing stroke risk
- List 2 components of integrative care for stroke
- Discuss the role of mindfulness on stroke risk factors
- Know resources for investigating primary research in integrative medicine

Outline

- Integrative Medicine
- Evidence of Benefit – Mediterranean Diet
- Emerging Evidence – Gut Microbia
- Controversies – Vit D and CV Risk
- Must Do's – Mindfulness
- Resources



Integrative Medicine

- National Institutes of Health:
  - Integrative medicine "combines mainstream medical therapies and CAM therapies for which there is some high-quality scientific evidence of safety and effectiveness."
- Dr. Andrew Weil :
  - "healing orientation" that takes into consideration the whole person (mind, body, spirit) as well as lifestyle

Evidence of Benefit: Mediterranean Diet

Definition of the Mediterranean Diet (MeD): at least two of the following seven components

1. HIGH RATIO OF MONOUNSATURATED TO SATURATED FAT
2. SOME RED WINE CONSUMPTION DEFINED AS LOW TO MODERATE
3. HIGH LEGUME CONSUMPTION
4. SIGNIFICANT GRAIN AND CEREAL CONSUMPTION
5. SIGNIFICANT CONSUMPTION OF FRUITS AND VEGETABLES
6. MODERATE CONSUMPTION OF MILK AND DAIRY PRODUCTS
7. LOW CONSUMPTION OF MEATS AND MEAT PRODUCTS WITH INCREASED FISH

Rees K et al., 2013

MeD: Early Findings of Benefit

- Seven Countries study in 60's found lower CV mortality rate in Mediterranean countries (Greece, Italy) compared to USA and Finland
- Early prospective studies found reduced CV morbidity & mortality
- More recent prospective cohort studies found dose response relationships -> the greater the adherence to MeD, the greater reduction in:
  - overall mortality
  - CV morbidity and mortality

MeD RTC: PREDIMED TRIAL

- **Eligibility** : 7447 subjects with either DM or 3 major CV RF (tobacco, HTN, elevated LDL, low HDL, obese, Fhx of early CAD)
- **Intervention**: Either MeD supplemental extra virgin olive oil (1 l/week) or MeD supplemental mixed nuts (30 gr/QD). Controls counseled on low fat diet. Dietician ran baseline and quarterly educational sessions.
- **Results**: Reduced **Composite Score** (MI, CVA, death from CV causes)
  - MeD & olive oil – (HR) 0.70 (95% confidence interval), 0.53 - 0.91)
  - MeD & nuts – 0.70 (0.53 to 0.94)
  - Overall RR 30%
- Reduced Stroke events in both groups
  - MD with olive oil & nuts respectively, 0.67 (0.46–0.98), 0.54 (0.35–0.84)

Estruch et al., 2006; Martinez-Gonzales et al., 2015

MeD RCT: CV Risk Factors Reduced

- Cholesterol/HDL
  - MeD with olive oil and nuts respectively, **–0.32** (–0.45 to –0.18), **–0.17** (–0.27 to –0.02)
- LDL – olive oil group
- Glucose (mg/dl)
  - MeD with olive oil and nuts respectively, **–3.8** (–7.4 to –0.2), **–2.5** (–5.5 to 0.5)
- Systolic BP - (mean change from baseline)
  - MeD with olive oil and nuts respectively, **– 4.8 mm**Hg (–6.7 to –2.7), **– 6.5 mmHg** (–8.7 to –4.3)
- Diastolic BP
  - MeD with olive oil and nuts respectively, **–2.5 mmHg** (–3.5 to –1.5), **–3.6 mmHg** (–4.7 to –2.5)
- CRP – olive oil group
- IL6 – both MeD diet groups

Estruch et al., 2006; Martinez-Gonzales et al., 2015

MeD Compliance and Incidence of Stroke

- REGARDS Study - Prospective Cohort Study of 30239 subjects
- "Stroke belt" of US oversampled
- Baseline Food Frequency Questionnaire
  - MeD adherence computed as low, moderate, high
  - Low adherence group was used as "reference" or control
- Telephone interview Q 6 months to eval for CVA
- Followed for 6.5 years

Howard et., 2006; Tsivgoulis et al., 2015

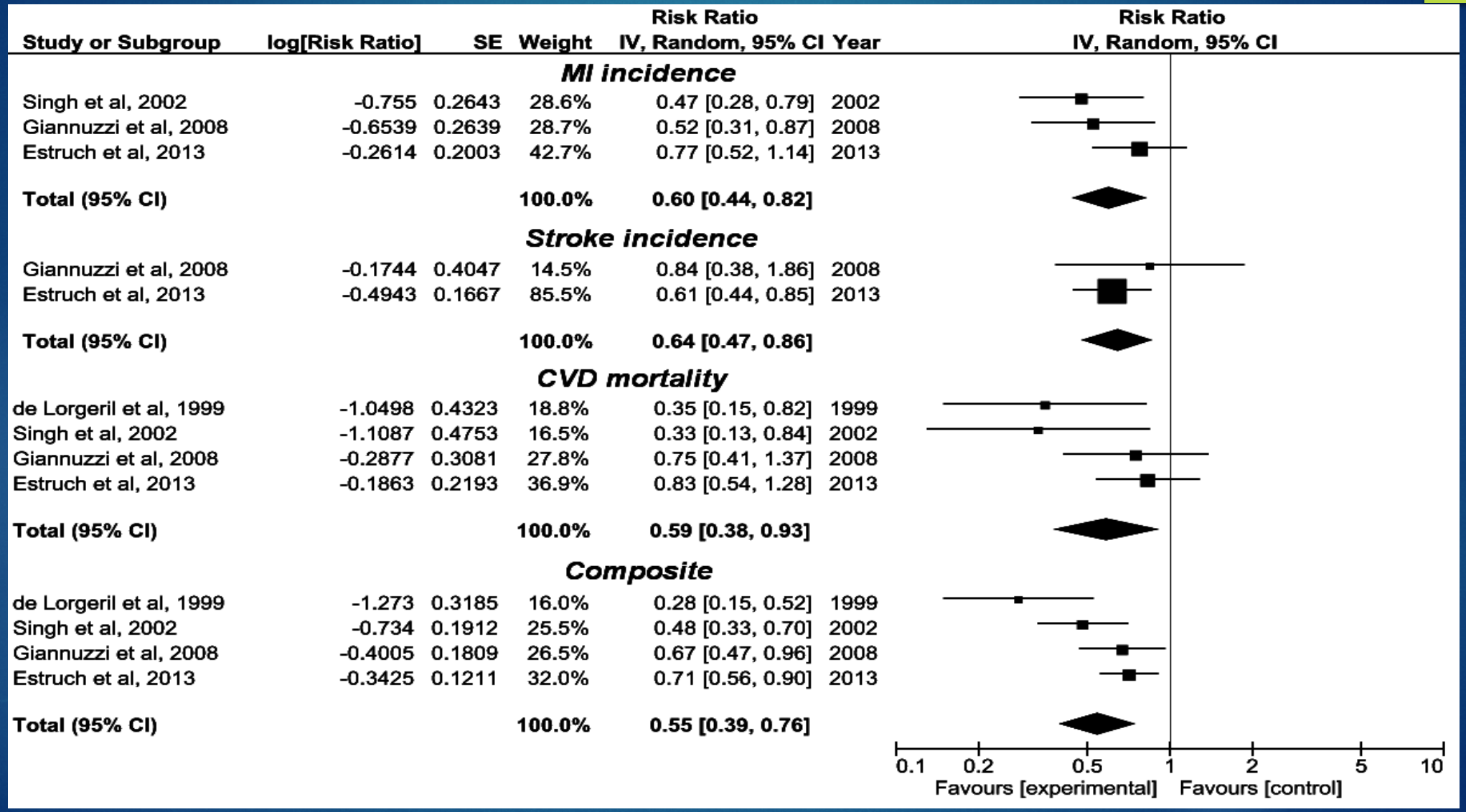
Association of MeD Adherence Stratified by Tertiles With Incident Ischemic Stroke

	Low Adherence (MeD Score, 0–3); n=6632 nstrokes=167	Moderate Adherence (MeD Score, 4–5); n=8354 nstrokes=222	High Adherence (MeD Score, 6–9); n=5211 nstrokes=108
Crude	Reference	HR=1.03 (95% CI, 0.84–1.26); *P*=0.779	HR=0.78 (95% CI, 0.61–1.00); *P*=0.047
Model I	Reference	HR=0.94 (95% CI, 0.77–1.15); *P*=0.559	HR=0.69 (95% CI, 0.54–0.88); *P*=0.003
Model II	Reference	HR=0.97 (95% CI, 0.80–1.19); *P*=0.802	HR=0.73 (95% CI, 0.57–0.94); *P*=0.013
Model III	Reference	HR=1.00 (95% CI, 0.82–1.23); *P*=0.996	HR=0.76 (95% CI, 0.60–0.98); *P*=0.034
Model IV	Reference	HR=0.96 (95% CI, 0.78–1.20); *P*=0.752	HR=0.78 (95% CI, 0.60–1.01); *P*=0.057

•Model I adjusts for age, race, age-race interaction, region, sex. Model II adjusts for age, race, age-race interaction, region, sex, income, education. Model III adjusts for age, race, age-race interaction, region, sex, income, education, total energy, smoking status, sedentary behavior. Model IV adjusts for age, race, age-race interaction, region, sex, income, education, total energy, smoking status, sedentary behavior, history of heart disease, atrial fibrillation, BMI, waist circumference, DM, HTN, HTN medication use, systolic and diastolic blood pressure.

Tsivgoulis et al., 2015

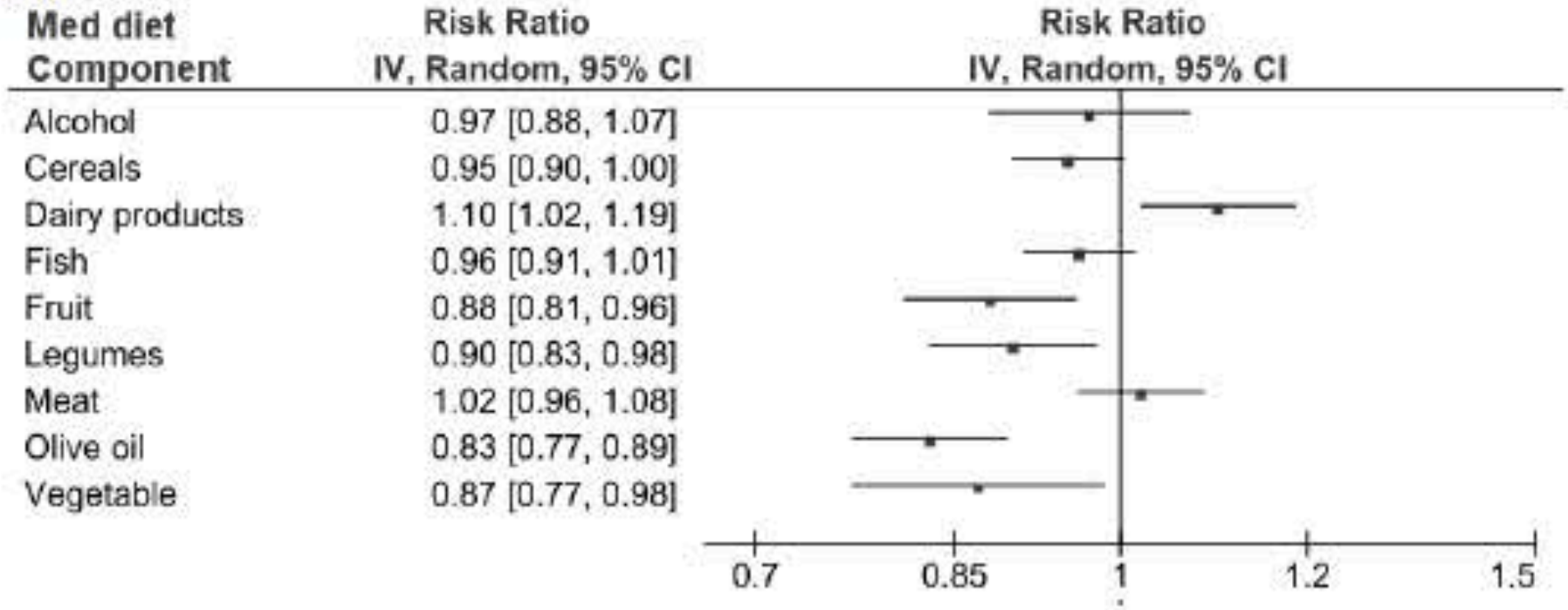
Meta-analysis: MeD Adherence and CV Outcomes in RCT



Grosso et al., 2015

Meta-analysis: MeD Components & Composite CVD

Figure 4. Pooled risk ratios of individual Mediterranean diet components and composite CVD outcomes.



Grosso et al., 2015

Implications for MeD & Stroke

- PREDIMED Trial found significant reduction in composite score of MI, stroke and CV mortality
- MeD diet significantly decreased stroke (of the 3 in composite score)
- MeD diet benefit found to influence outcomes in dose dependent manner, the more compliant with diet the greater the benefit
- Meta-analysis she benefit for MI, stroke and CV mortality
- Meta-analysis show major food group contributors:
  - Legumes
  - Fruits, Vegetables
  - Olive Oil
  - +/- complex grains

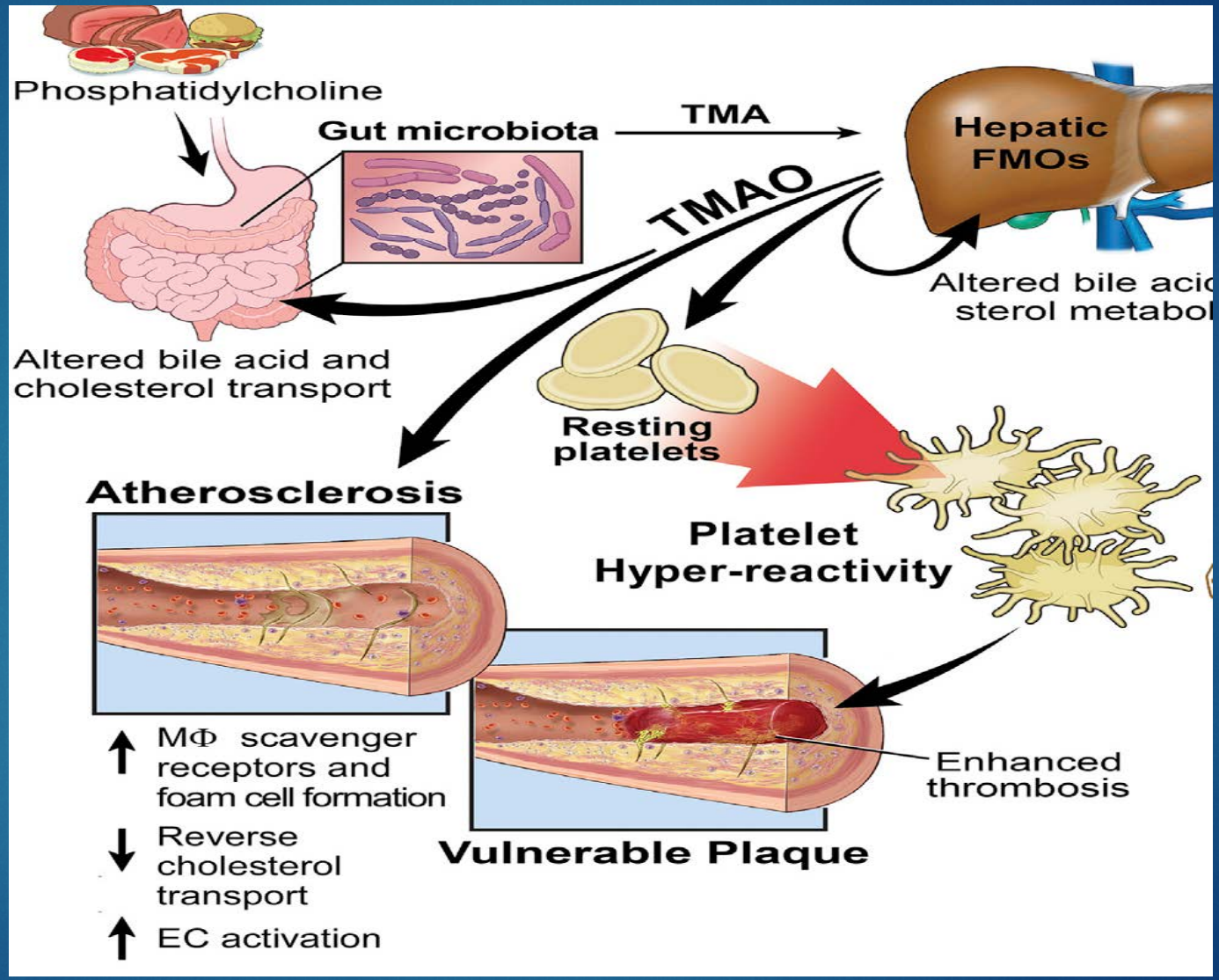
Emerging Evidence: Gut Microbia and Stroke

Integrative Medicine Paradigm for Gut

- Major immune organ
- Stress (psychological or physiological) causes alterations in gut microbia and gut barrier
- Once gut barrier is compromised large proteins are passed and activate immune system
- This alteration of gut microbia then causes systemic effects
- Gut motility dysfunction also causes gut microbia alteration

Trimethylamine Diet and Gut Microbia

Trimethylamine (TMA)-containing nutrients (phosphatidylcholine, choline, and carnitine) are used by gut microbes as a carbon fuel



TMAO increases platelet (Plt) aggregation in human serum and to immobile collagen tissue under shear force (in vitro)

TMAO increases in vivo thrombosis in mouse carotid

Wu et al., 2016

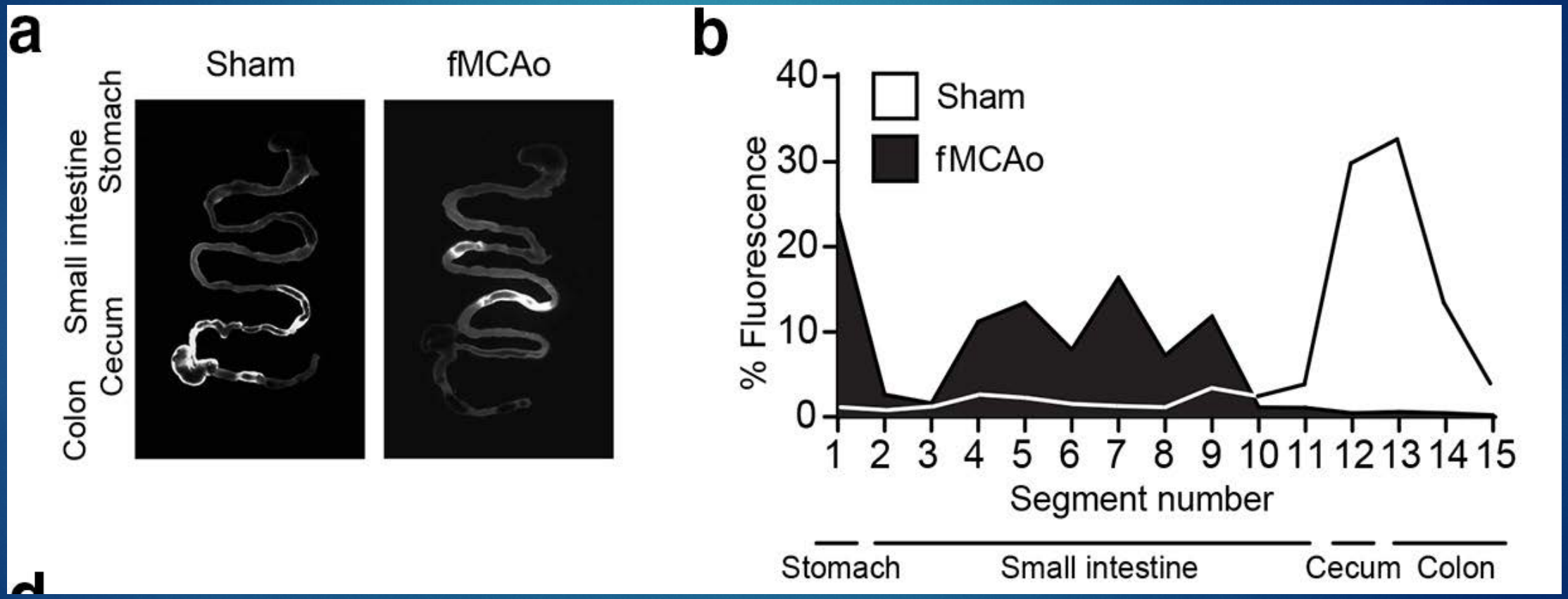
Emerging Evidence: Gut Microbia and Platelet Aggregation

- High choline diets and subsequent TMAO levels were associated with specific gut microbia
- High TMAO levels and platelet aggregation is transferable with FMT
- Prospective observation study in > 4,000 patients followed in cardiology clinic -> dose response relationship between TMAO blood levels and 3 yr CV event rate (MI, CVA, death, revascularization)

Wu et al., 2016

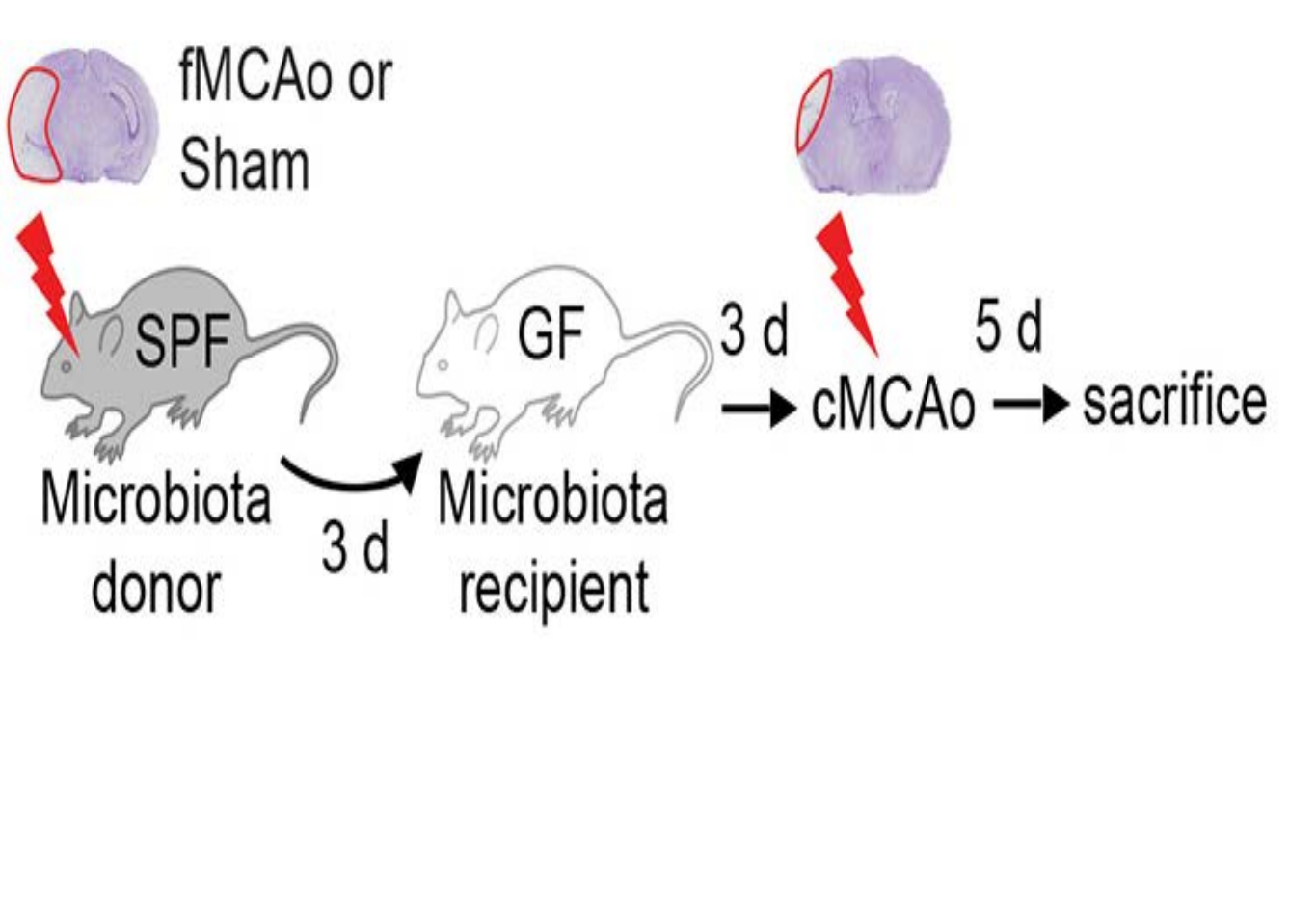
Emerging Evidence: Gut Dysbiosis & Stroke

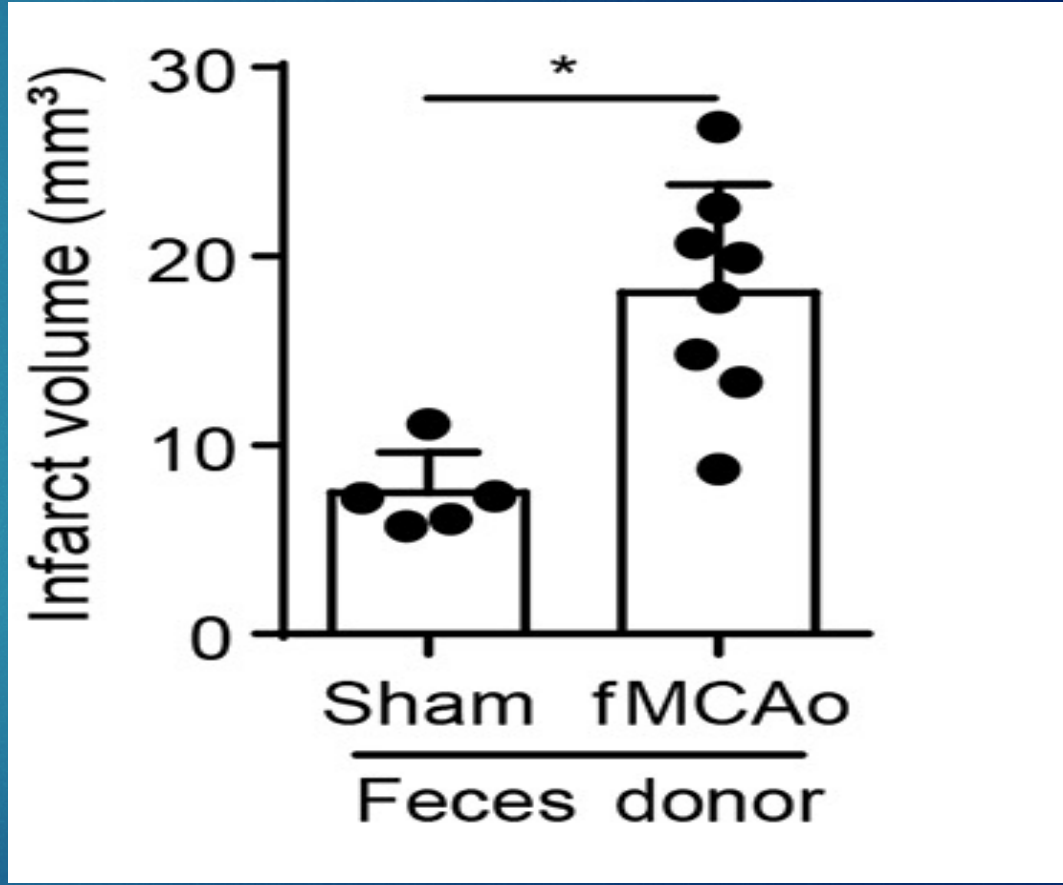
- 3 day post MCA ischemic stroke -> decreased gut microbia diversity
  - Firmicutes, Bacteroidetes, and Actinobacteria
- Stroke -> significantly reduced gut motility compared to sham



Singh V et al., 2016

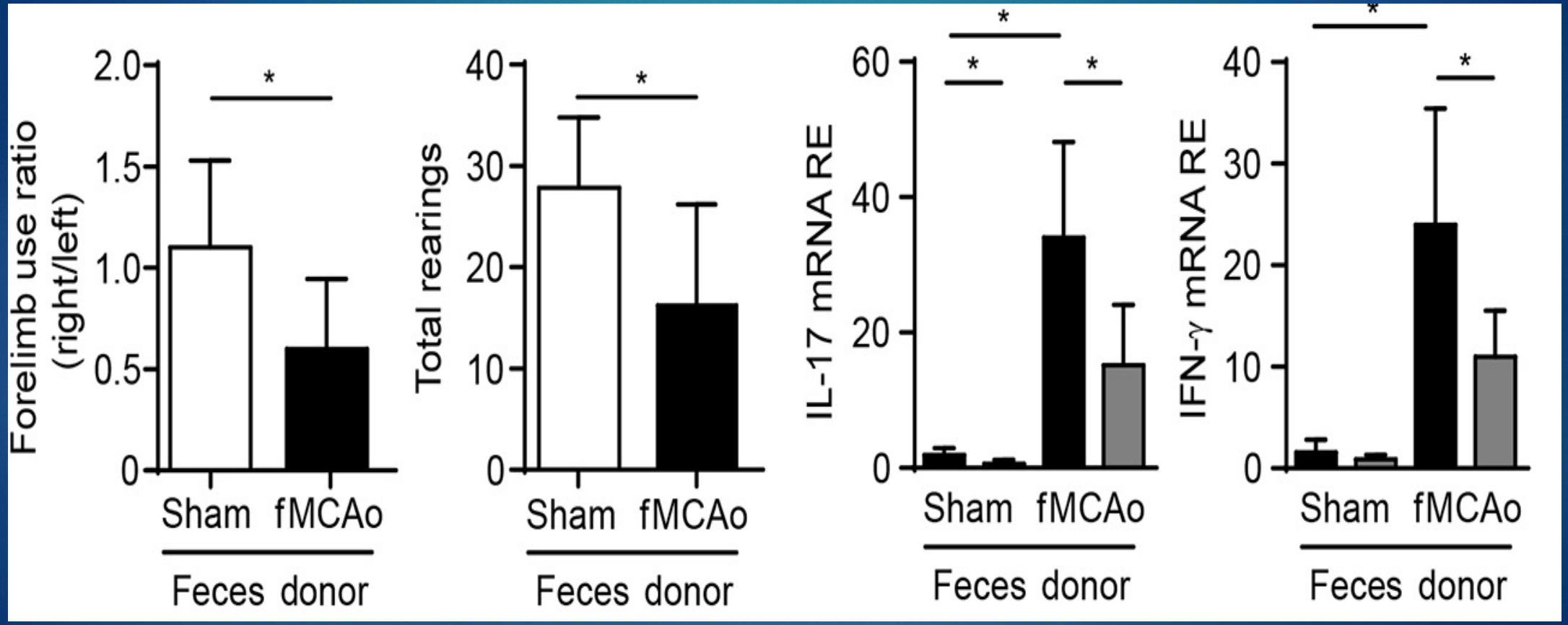
Microbiota Transplantation (FMT) from Stroke Mice Worsens Outcome





Singh V et al., 2016

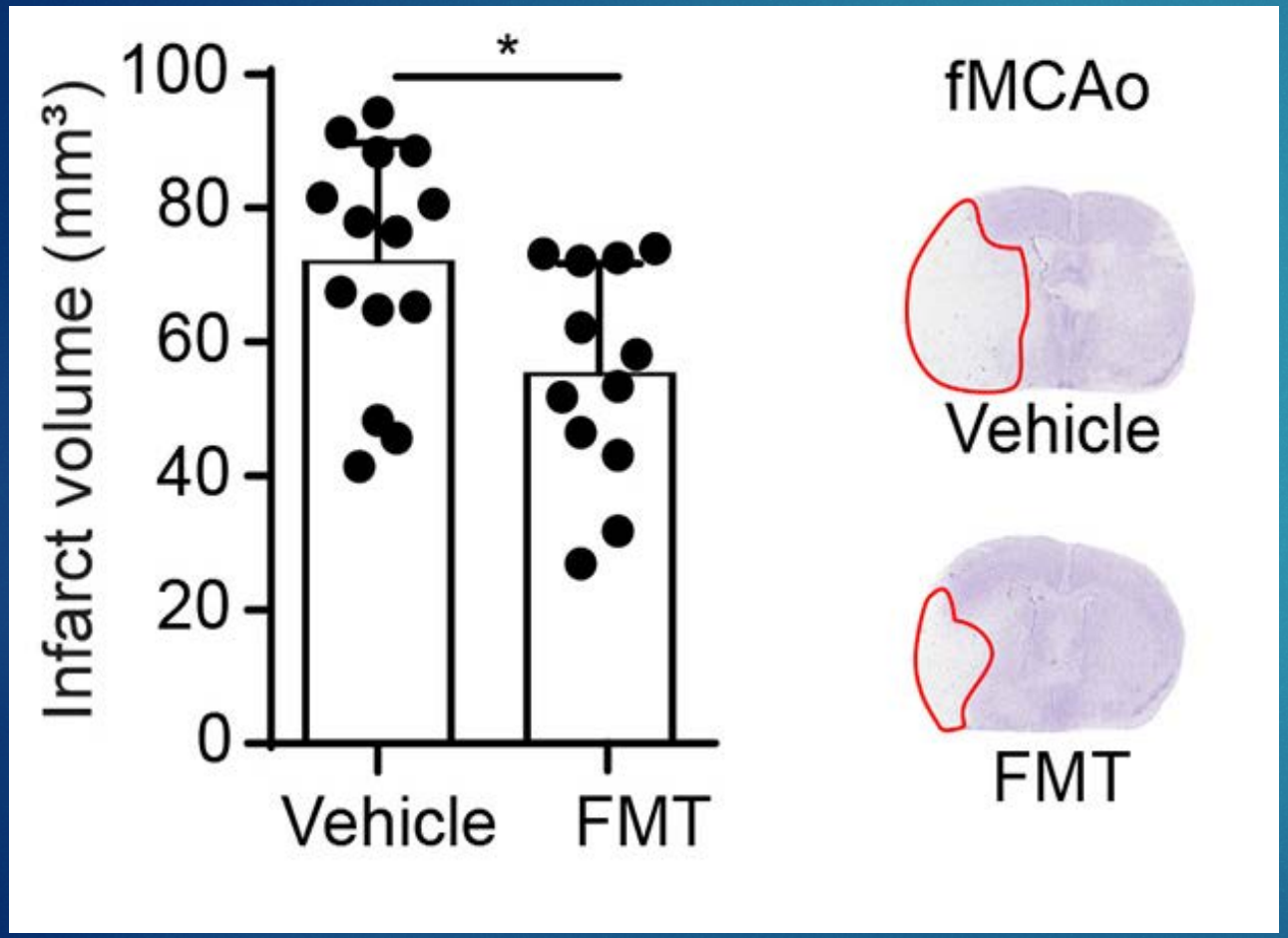
Behavioral & Immunological Outcomes After Either Sham or Stroke FMT

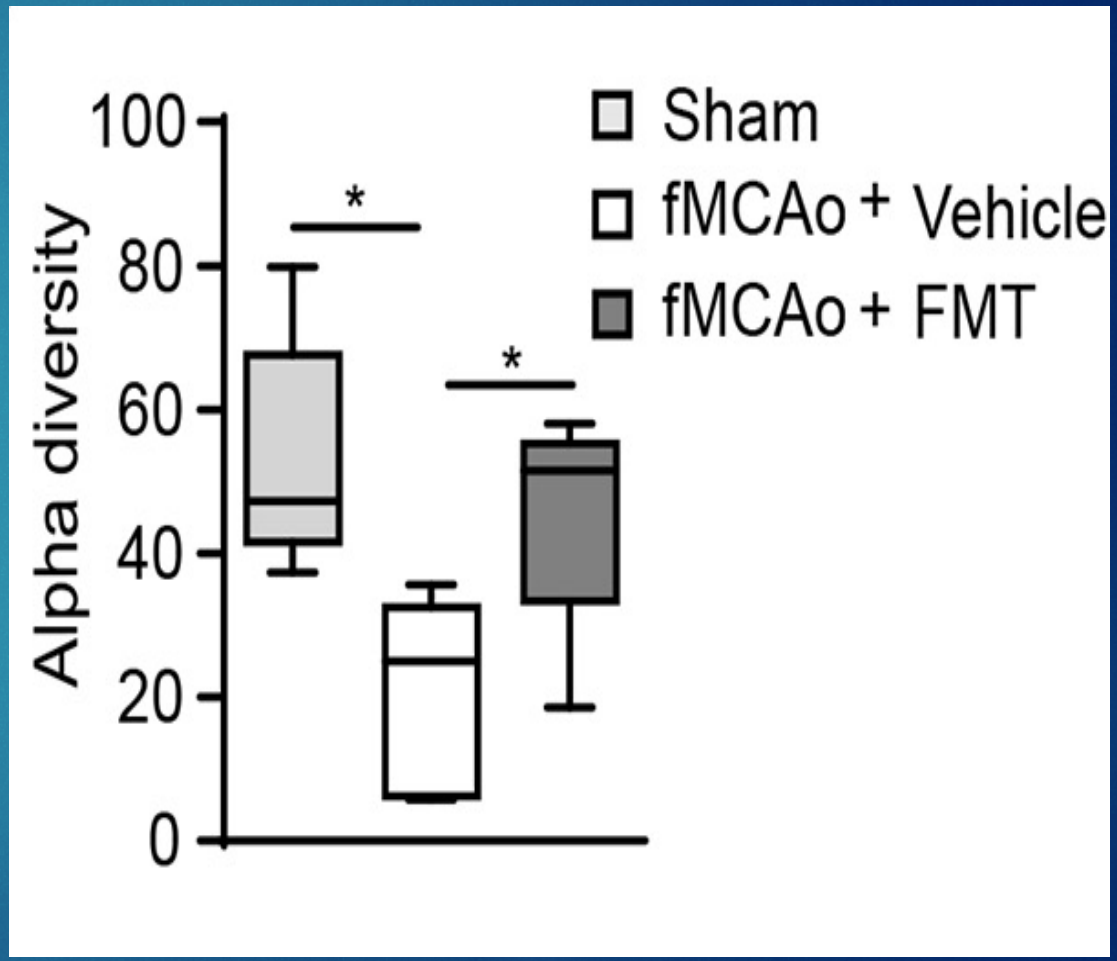


Singh V et al., 2016

Healthy FMT Protective in Stroke

- Healthy FMT vs Vehicle given Day 1 of MCA Stroke





Singh V et al., 2016

Implications for Gut Microbia in Stroke

- High Choline Diet increases gut microbia that favor Plt aggregation, carotid artery stenosis and further alterations in gut microbia favoring more 'harmful' populations
- Stroke alters gut microbia and motility in animal model that is associated with larger stroke volume and poorer motor outcomes
- Poorer stroke outcome can be induced with FMT
- FMT can be neuroprotective if given within first day of stroke reducing stroke volume and increasing gut microbia variability

Controversies: Vit D and CV Risk

Vit D Implications on CV Benefit

- Background
  - CV events higher in countries furthest from equator and of higher altitude
  - More CV events reported in winter months
- Physiological Data
  - Vit D receptor (VDR) -/- mice have increased renin receptor, AII, & aldosterone (RAS activation).
  - RAS activation normalized with 1-25(OH)D
  - VDR -/- mice -> ventricular hypertrophy & HTN, which is reversed with Vit D supplementation
  - Enzymatic, nutritional or VDR deficiencies -> increased atherosclerosis, thrombosis, and peripheral vascular resistance in rodents
  - Implicated in murine vascular tone modulation via Ca^{+} and COX-1
  - Promotes carotid artery repair (reendothelialization) in diabetic mice
  - Anticoagulant properties by reducing inhibition of plasminogen activator

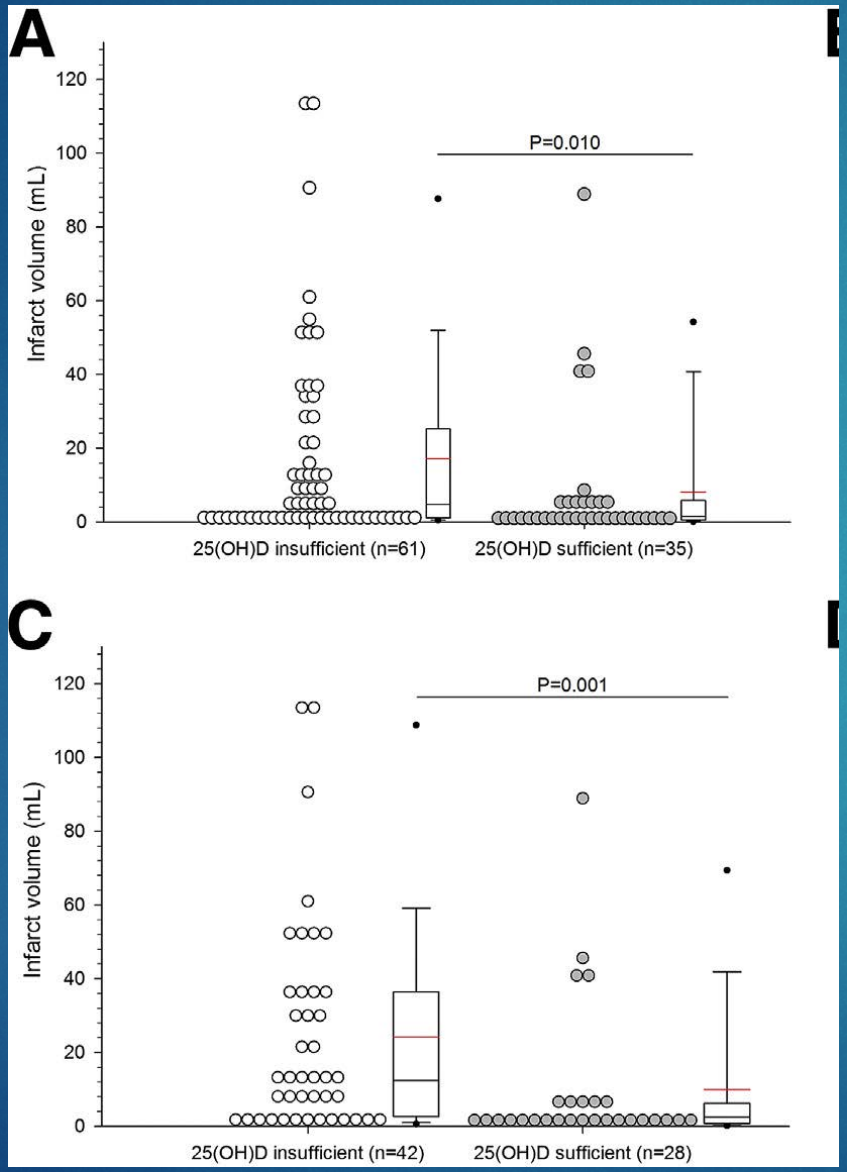
Vit D: Observational Studies

- Low 25(OH)D correlated with :
  - Increased Hypertension (Women's Health Study, Health Professional's Followup & Nurses' Health Study)
  - Peripheral Vascular Disease (National Health and Nutritional Examination Survey)
  - Myocardial Infarction (Health Professional's Follow-up)
  - Cardiovascular Mortality (prospective cohort study of patient going for angiography)
  - Fatal Stroke (Ludwigshafen Risk and Cardiovascular Health Study)
  - Cardiovascular Disease (Framingham Cohort; only in hypertensive patients)
  - Fatal Cardiovascular Events & Early Death (Copenhagen City Heart Study)
  - Ischemic Stroke (Umbrella meta-analysis)

Vit D: Supplementation RCT

- 2800 IU x 8 weeks -> no effect:
  - Systolic or diastolic BP, HDL, Renin or Aldosterone
- 800 IU x 24-62 months 70 yo -> no effect
  - Stroke Mortality, CV Mortality, All Cause Mortality
- 400 & 1000 IU -> no effect
  - CV events or Stroke
- Meta-Analysis of RCT -> no effect
  - Stroke, MI, mortality,
  - Surrogate outcomes - lipid fractions, glucose, systolic or diastolic BP
- VITAL Trial
  - RTC of 25,875 US sample to receive 2000 IU D3, OM3FA, both or placebo
  - Treatment duration 5 yrs
  - Outcome = cancer and CV Events (MI, Stroke, CV death)

Vit D: Stroke Outcomes



- Vit D significantly inversely related to infarct volume (A) and infarct type (lacunar stroke) (C)
- Risk for a 90 day poor modified Rankin Scale score (3-6) was doubled with every 10 ng/mL decrease in 25(OH)D level (table not shown)

Turetsky et al., 2015

Implications for Vit D in Stroke

- While physiological and observational studies support a role for Vit D in stroke, the RCT with Vit D supplementation have not supported a role for Vit D supplementation and stroke prevention
- VITAL Trial data with larger sample size and adequate Vit D supplementation, will start reporting findings in 2017
- Early data suggest Vit D may be related to stroke volume and 90 day clinical outcomes

Must Do's: Mindfulness

Must Do's: Mindfulness

- Mindfulness is the nonjudgmental attention to the present moment

- Significantly reduced depression, anxiety, headache, pain in medical and non-medical patients

Kabat-Zinn, 1990

Mindfulness & Stroke

- Improvement in depression and anxiety depending on study design
- No significant improvement in BP for stroke
- Clear improvement in Quality of Life scales

Abbott et al., 2014: Lawrence et al., 2013

Mindfulness Increases QOL Measures

Table 9 Perceived general health and quality of life

Study	Measure	Pretest mean (SD)	Posttest mean (SD)	Follow-up mean (SD)	*P* value
Moustgaard *et al.* (46)	SF-36 PCS	39·19 (6·21)	46·78 (7·73)	45·73 (8·74)	0·001
	SF-36 MCS	48·55 (10·14)	56·10 (6·40)	53·95 (10·60)	0·002
	SS-QoL (total)	285·95 (37·05)	321·81 (38·31)	326·19 (38·94)	0·001
	SS-QoL Energy	12·24 (4·13)	15·24 (3·83)	15·86 (3·93)	0·001
	SS-QoL Family role	27·57 (8·75)	31·0 (7·74)	31·48 (7·35)	0·001
	SS-QoL Mobility	45·38 (12·10)	49·71 (10·28)	50·48 (10·13)	0·004
	SS-QoL Mood	29·91(6·95)	33·62 (5·60)	33·57 (5·15)	0·013
	SS-QoL Personality	11·48 (5·14)	16·38 (3·57)	16·81 (3·40)	0·001
	SS-QoL Self-care	34·67 (4·31)	36·57 (3·76)	36·57 (3·92)	0·001
	SS-QoL Social roles	19·76 (7·85)	25·29 (6·07)	26·10 (5·82)	0·001
	SS-QoL Thinking	11·29 (3·12)	14·43 (2·25)	14·81 (2·11)	0·001
	SS-QoL Upper extremity	36·33 (8·57)	38·57 (7·93)	38·86 (7·95)	0·007
	SS-QoL Vision	16·76 (4·56)	17·71 (3·81)	17·95 (3·32)	0·017
	SS-QoL Work	8·91 (3·46)	10·76 (3·25)	10·95 (3·19)	0·001

MCS, mental component score; PCS, physical component score; SF-36, 36-Item Short-Form General Health Survey; SS-QoL, Stroke Specific Quality of Life Scale.

Lawrence et al., 2013

Implications for Mindfulness & Stroke

- In stroke as with other medical populations, mindfulness decreases anxiety & depression
- QOL significantly improved in stroke patients who participated in mindfulness practice including:
  - Energy
  - Self Care
  - Upper extremity use

Resources for Integrative Medicine

- National Center for Integrative and Complementary Health
  - https://nccih.nih.gov/research/results/spotlight
- Natural Medicines
  - https://naturalmedicines.therapeuticresearch.com
- Consumer labs
  - https://www.consumerlab.com

Summary

- MeD has observational and RCT evidence for risk reduction of stroke and mortality
- Gut microbia increase Plt aggregation in serum and endothelial surface, and increases atherosclerosis in animal models
- Animal studies show gut microbia and motility significantly altered in stroke. This altered microbia increase stroke severity in FMT. Healthy FMT can be protective if given early in stroke
- While RTC outcomes thus far on role of Vit D in stroke is still forthcoming, there is implication for lower Vit D and poorer stroke outcome
- Mindfulness practice may improve overall QOL but especially consider in patients with low energy, upper extremity weakness.

Thank You

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