1). MCP Bases of Transition from Disease to Health

1. Two Critical Tools – Imaging, Genetics

2. Three Behavioral Ages - Elderly, Mid Life, Children

3. Two Historical Paths – B. Blockers, ACE / ARBs / ARNI

4. Two Historical Paths – Statins / PCSK9i, SGLT2i / GLP1-RA

Cardona, July 15, 2019

No Disclosures
CVD Mortality Trends For Males And Females
(United States: 1979–2015)

AHA Councils (EJ Benjamin et. al.) Circulation. 2018;137:e67
Cardiovascular Disease Undertreatment At Each Stage of The Disease

Large missed opportunities at every step in prevention and treatment of cardiovascular disease

- Failure to Make Risk Factor Modifications
  - Can reduce odds of CVD by 80%.

- Failure to Elicit & Follow People’s Goals & Needs
  - Higher patient activation levels lead to better healthcare experiences.

- Failure to Diagnose
  - 20-40% of heart attacks occur in undiagnosed CVD patients.
  - 20% undiagnosed HTN.
  - 30% undiagnosed hyperlipidemia

- Failure to Use Proven First Line Treatments
  - 43-67% of patients nonadherent to statins after 1 year.
  - Over half of AF patients not on therapeutic anticoagulation.

- Failure to Use Advanced Treatments
  - 1/3 prescribed PCSK9s get Rx approved and filled.
  - Variation in major CV procedures.

- Failure to Provide Supportive Care
  - 5% of severe heart failure patients receive palliative care.

AHA - M McClellan et. al. Circulation. 2019;139:e44
From Aging / Disease to Youth / Health

2005 - 2019

Primary
25-50 yrs

Secondary
50-100 yrs

Primordial
00-25 yrs

1) DEMENTIA
2) Longevity
3) Longevity 50/50
4) HRP PESA AWHS
5) IIIP
6) SHE
7) HARLEM NY - NIH VILLAGE

CABG - ASA Imaging-MRI PCI- Rapamycin FREEDOM
A Health Center In The Adult Brain (?)

To Stimulate / Motivate

NHLBI Kenya Model -BP

GHS, Cardona, Spain

JACC 2016; 67:476
From Aging / Disease to Youth / Health

2005 - 2019

Secondary
50-100 yrs

Primary
25-50 yrs

Primordial
00-25 yrs

1) CABG - ASA
2) PCI - Rapamycin
3) FREEDOM

1) DEMENTIA
2) LONGEVITY
3) IIIP
4) HRP
5) PESA
6) SHE
7) HARLEM NY - NIH VILLAGE

From Aging / Disease to Youth / Health
Barriers To Access (Red) To CV Medication and Solutions Provided By The Polypill (Orange)

Factors Reported To Affect Adherence:

Patient:
- Socioeconomic status
- Educational level
- Social support
- Depression

Health Care System:
- Availability
- Affordability
- Lack of incentives

Disease or Condition:
- Chronicity
- Duration
- Absence of symptoms

Treatment:
- Polypharmacy
- Numbers of pills
- Constant changes
- Complexity

Dependence

Improve availability and affordability

Polypill

Control of Risk Factors

Reduction of CV events?
### ADHERENCE AND RISK FACTOR CONTROL?

**Risk Factors - Proportion of Participants at Goal % – 1 year**

<table>
<thead>
<tr>
<th>Trials</th>
<th>LDL</th>
<th>SBP</th>
<th>DBP</th>
<th>Hb A1C</th>
<th>Meet Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base FU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BARI-2D</td>
<td>75</td>
<td>56</td>
<td>70</td>
<td>52</td>
<td>14</td>
</tr>
<tr>
<td>COURAGE</td>
<td>51</td>
<td>55</td>
<td>55</td>
<td>59</td>
<td>12</td>
</tr>
<tr>
<td>FREEDOM</td>
<td>55</td>
<td>63</td>
<td>53</td>
<td>55</td>
<td>12</td>
</tr>
</tbody>
</table>

Freedom, Bari-2D, Courage Investigators, JACC 2013;61:1607
PURE (S Yusuf et al.) Lancet 2011; Aug 28 - Poor Countries, 7% !!!
NHANES, AHA, NHLBI-JNC-7, NHLBI-NCEP – Significant < Adherence
Among 2,588 U.S. outpatients with chronic HFrEF in the CHAMP-HF registry with complete medication data and no contraindications to medical therapy, use and dose were examined at baseline and at 12-month follow-up. Most eligible HFrEF patients did not receive target doses of medical therapy at any point during follow-up, and few patients had doses increased over time.

CNIC- Polypill, 2ary Prevention.

FOCUS 1 & 2
Argentina
Brazil
Paraguay
Italy
Spain

FREEDOM
AETNA-DIABETES
SECURE-EC 2015

Am. H J 2011;162:811
JACC, 2014; 64:2071
BMC Pharmac. Toxic. 2017;18:10

HOPE-3-NEJM 2016;374:2032 – Polypill for 1ary Prevention?

Approved in 45 Countries

FOOD INTERACTION
PHARMACOKINETIC INTERACTION WITH ASPIRIN
PHARMACOKINETIC INTERACTION WITH SYMVASTATIN
PHARMACODINAMIC INTERACTION WITH RAMIPRIL
PHARMACODYNAMIC INTERACTION WITH RAMIPRIL
PHARMACODYNAMIC INTERACTION WITH SYMVASTATIN
BIO-EQUIVALENCE

ASA, Statin, ACE-Inhibitor
A consensus statement has been developed by Inter-American Society of Cardiology with the aim of answering some important questions related to CVD in this region and the role of the polypill in CV prevention. Clinical scenarios in which the polypill could represent an effective intervention in primary and secondary CV prevention are described. This initiative is expected to help professionals involved in the management of CVD and public health policymakers develop optimal strategies for the management of CVDs.
Indications For Use of The Polypill In Primary And Secondary Prevention

Primary prevention
- Patients with a high or very high CV risk determined by risk charts.
- Diabetic patients older than 50 yrs and at least 1 associated risk factor: smoking, hypertension, dyslipidemia, high LDL-C, or microalbuminuria.
- Diabetic patients older than 50 yrs with chronic renal disease and macroalbuminuria or microalbuminuria.

Secondary prevention
- Acute myocardial infarction
- Acute coronary syndromes
- Stable coronary artery disease
- Peripheral artery disease
- Stroke
- Symptomatic and asymptomatic LVD and high CV risk
Overview of Deprescribing by the Cardiovascular Clinical Team

From Aging / Disease to Youth / Health

2005 - 2018

Secondary
50-100 yrs

Primary
25-50 yrs

Primordial
00-25 yrs

1) DEMENTIA
2) DEMENTIA
3) LONGEVITY
4) HRP
5) IIIP
6) SHE
7) HARLEM NY - NIH VILLAGE

50/50

CABG - ASA
Imaging-MRI
PCI - Rapamycin
FREEDOM
THE SCIENCE OF A LONG LIFE

DR. VALENTIN FUSTER
JOSEP CORBELLA

WITH A FOREWORD BY RAFAEL NADAL AND PAU GASOL
4). Environment & Risk Factors

AV Khera, V Fuster, PM Ridker et al., NEJM 2016; 375:2349
Crude Weighted Trends in Screen-Based Sedentary Behaviors Among the US Population, NHANES 2001-2016

A Sitting watching television or videos

Age, 5-11 y

All $P$ for trend < .01, decrease

Prevalence, %

Year


1296 1139 1236 1140 1308 1378 1430 1415

Age, 12-19 y

All $P$ for trend > .05

Prevalence, %

Year


1990 1957 1097 1257 1141

Age, ≥20 y

Hours per day

≥2 ≥3 ≥4

Prevalence, %

Year


4008 4155 4599 4724 4542

No. of participants

L Yang, Y Cao et. al. JAMA 2019;321:1587
It is unclear what level of moderate to vigorous intensity physical activity (MVPA) offsets the health risks of sitting. A total of 8,689 deaths (1,644 due to CVD) occurred among 149,077 participants over an 8.9-year (median) follow-up. Sitting is associated with all-cause and CVD mortality risk among the least physically active adults; moderate / vigorous physical activity doses with the current recommendations attenuate or effectively eliminate such associations.

E Stamatakis, D Ding et al., J Am Coll Cardiol 2019; 73:2062 (Sydney)
Sitting and Physical Activity Time and All-Cause Mortality Events

E Stamatakis, D Ding et. al. J Am Coll Cardiol 2019;73:2062 (Sydney)
Atherosclerotic Plaque Burden Measured By 3DVU According To Sleep Duration And Quality

We estimated the durations of total daily sleep and daytime naps based on the amount of time in bed and self-reported napping time events in 116,632 participants from seven regions. Estimated total sleep duration of 6-8 h per day is associated with the lowest risk of deaths and major CV events. Daytime napping is associated with increased risks of major CV events and deaths in those with >6 h nighttime sleep but not in those ≤6 h/night.

Estimated Total Daily Sleep Duration And The Composite Of Total Deaths And Major CVD

PURE (C Wang, S Yusuf et. al.) Eur Heart J. 2019;40:1620
Sleep disruption promotes Alzheimer's pathology

Sleep is accompanied by lowered activity-driven release and heightened clearance of Aβ and tau from the brain. Sleep deprivation reduces aggregate clearance and promotes astroglisis, network activity-driven tau and Aβ release, further protein aggregation, and the spread of Alzheimer's disease pathology.

Regular sleep-wake cycle vs. Sleep deprivation

- Celestial astrocyte
- Inflammatory astrocyte
- Astrocyte
- Aβ aggregate
- Tau aggregate
- Aβ
- Tau

Ventricle

Clearance of extracellular proteins

Synaptic activity-driven release of tau and Aβ

4). Environment & Risk Factors

AV Khera, V Fuster, PM Ridker et al., NEJM 2016; 375:2349
Current dietary intakes of North Americans are inconsistent with the Dietary Guidelines for Americans. A key step in creating a healthier and more sustainable food system is to build innovative system-level approaches that improve individual behaviors, strengthen industry and community efforts, and align policies with evidence-based recommendations. To enable healthier food and favorably impact CV health, immediate action is needed to promote favorable innovation at all levels of the food system.

CAM Anderson, C Spees et al., Circulation 2019; 139:e1025
Multiple Stakeholders Contribute To A Healthy, Sustainable Food System

CAM Anderson, C Spees et al. Circulation. 2019;139:e1025
# Menu Calorie-Labeling Timeline

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 3</td>
<td>NYC Board of Health implements labeling after policy revised and supportive court judgment</td>
</tr>
<tr>
<td>March 9</td>
<td>FDA announces delay to 1 year after industry guidance released, to comply with 2016 omnibus appropriations bill</td>
</tr>
<tr>
<td>March 30</td>
<td>Affordable Care Act passes, with Section 4205 creating a federal calorie-labeling requirement</td>
</tr>
<tr>
<td>April 6</td>
<td>FDA publishes proposed rule on labeling</td>
</tr>
<tr>
<td>December 1</td>
<td>FDA publishes final rule and sets compliance date of December 1, 2015</td>
</tr>
<tr>
<td>May 4</td>
<td>FDA announces delay in implementation to May 7, 2018</td>
</tr>
<tr>
<td>May 5</td>
<td>FDA releases final industry guidance</td>
</tr>
<tr>
<td>May 7</td>
<td>FDA requires implementation of calorie labeling nationwide</td>
</tr>
<tr>
<td>February 6</td>
<td>U.S. House passes Common Sense Nutrition Disclosure Act</td>
</tr>
<tr>
<td>September 26</td>
<td>FDA enters into a legal agreement with CSPI and others to enforce labeling in May 2018</td>
</tr>
</tbody>
</table>

**2006**

- **December 5**: NYC Board of Health passes first-choice labeling regulation and is sued by restaurant industry

**2008**

- **January 1**: Seattle/King County implements labeling

**2009**

- **March 30**: Affordable Care Act passes, with Section 4205 creating a federal calorie-labeling requirement

**2010**

- **April 6**: FDA publishes proposed rule on labeling

**2011**

- **December 1**: FDA publishes final rule and sets compliance date of December 1, 2015

**2014**

- **July 9**: FDA moves compliance date to December 1, 2016, giving industry more time to implement

**2015**

- **May 5**: FDA releases final industry guidance

**2016**

- **May 4**: FDA announces delay in implementation to May 7, 2018

**2017**

- **May 7**: FDA requires implementation of calorie labeling nationwide

**2018**

- **February 6**: U.S. House passes Common Sense Nutrition Disclosure Act
- **September 26**: FDA enters into a legal agreement with CSPI and others to enforce labeling in May 2018
Global Diet and Health

NG Forouh et. al. Lancet. 2019;393:1916
The REGARDS trial is a prospective cohort of black and white adults followed from 2003 to 2007 through 2014. Inclusion criteria included completion of a food frequency questionnaire and no baseline CAD or HF. Five dietary patterns (convenience, plant-based, sweets, Southern, and alcohol/salads) were derived from principal component analysis. The primary endpoint was incident HF hospitalization. This study included 16,068 participants (mean age 64.0). After a median of 8.7 years of follow-up, adherence to a plant-based dietary pattern was inversely associated with HF risk, whereas the Southern dietary pattern was positively associated with incident HF risk. The association was attenuated and no longer statistically significant after further adjusting for body mass index in kg/m², waist circumference, hypertension, dyslipidemia, diabetes mellitus, AF, and CKD.

Dietary Patterns Among American Adults And Risk For Heart Failure

- **Plant-Based**: cruciferous vegetables and other vegetables, fruit, beans, and fish
  - Risk of Heart Failure

- **Southern**: fried food, organ meats, processed meats, eggs, added fats, and sugar-sweetened beverages
  - Risk of Heart Failure

- **Convenience**: meat dishes, pasta, Mexican dishes, pizza, fried potatoes, Chinese dishes and fast food
  - No Association with Heart Failure Risk

- **Sweets**: desserts, bread, sweet breakfast foods, chocolate, candy, solid fats and oils, and miscellaneous sugar

- **Alcohol and Salads**: wine, liquor, beer, leafy greens and salad dressing

*KM Lara, RS Rosenson et. al. J Am Coll Cardiol 2019;73:2036 (Mount Sinai, NY)*
1). Intestinal Microbiota & its Metabolic Contributions to CV Health and Disease

2) **Impact Of Genetics And Epigenetics On Cardiovascular Phenotype**

S Costantino, F Paneni et. al. Eur Heart J. 2018;39:4150
Environmental Factors & Epigenetics

S Costantino, F Paneni et. al. Eur Heart J. 2018;39:4150
Main Epigenetic Mechanisms Modulated By Dietary Cardioprotection Compounds Animal Models And Humans

Dietary Patterns Feeding the Epigenome for Cardioprotection

We examined meat, fish, dairy products, and eggs and risk for IHD in the pan-European EPIC cohort (European Prospective Investigation Into Cancer and Nutrition). In this prospective study of 409,885 men and women in 9 European countries, diet was assessed with validated questionnaires and calibrated with 24-hour recalls. Lipids and blood pressure were measured in a subsample. During a mean of 12.6 years of follow-up, 7198 participants had a MI or died of IHD. Risk for IHD was positively associated with consumption of red and processed meat and modestly inversely associated with consumption of yogurt, cheese, and eggs, consistent with the associations of these foods with plasma non-high-density lipoprotein cholesterol and for red and processed meat with systolic BP could mediate such effects.

TJ Key et al., Circulation 2019; 139:2835
# Consumption of Meat, Fish, Dairy Prod., & Eggs Risk of Ischemic Heart Disease

Mutually-adjusted hazard ratios (95% CI) for first non-fatal MI or fatal IHD per increment in statistically calibrated intake of selected animal foods

<table>
<thead>
<tr>
<th>Food</th>
<th>Increment (g/day)</th>
<th>No. of cases</th>
<th>HR (95% CI)</th>
<th>HR &amp; 95% CI</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red and processed meat</td>
<td>100</td>
<td>7198</td>
<td>1.19 (1.06-1.33)</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Poultry meat</td>
<td>20</td>
<td>7198</td>
<td>0.99 (0.94-1.04)</td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>White fish</td>
<td>15</td>
<td>7198</td>
<td>1.01 (0.97-1.04)</td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Fatty fish</td>
<td>15</td>
<td>7198</td>
<td>0.96 (0.92-1.01)</td>
<td></td>
<td>0.091</td>
</tr>
<tr>
<td>Milk</td>
<td>200</td>
<td>7198</td>
<td>1.02 (0.99-1.06)</td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>Yogurt</td>
<td>100</td>
<td>7198</td>
<td>0.93 (0.89-0.98)</td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Cheese</td>
<td>30</td>
<td>7198</td>
<td>0.92 (0.86-0.98)</td>
<td></td>
<td>0.010</td>
</tr>
<tr>
<td>Eggs</td>
<td>20</td>
<td>7198</td>
<td>0.93 (0.88-0.99)</td>
<td></td>
<td>0.023</td>
</tr>
</tbody>
</table>

*TJ Key et. al. Circulation. 2019;139:2835*
In two large US cohorts, intake of SSBs was positively associated with total mortality showing a graded association with dose largely caused by CVD mortality, and a modest association was observed for cancer mortality. ASB intake was positively associated with total and CVD mortality but not cancer mortality at high intake levels, mostly among women and warrants further confirmation. ASBs could be used to replace SSBs among habitual SSB consumers but higher consumption of ASBs should be discouraged.

VS Malik, FB Hu et al., Circulation 2019; 139:2113
Dietary Frs. Among Adults Aged 25 Yrs or Older At The Global & Regional Level In 2017

GBD 2017 Diet Col. (A Afshin, CJL Murray et. al.)
Lancet 2019; 393: 1958
Mortality Rate Per 100,000 Pop. Attributed To Diet In 2017

Deaths per 100,000 population
- <105
- 105 to <142
- 142 to <189
- 189 to <249
- 249 to <313
- 313 to <397
- ≥397

DALY Rate Per 100,000 Pop. Attributed To Diet In 2017

Using 694 data sources of individual and population-level alcohol consumption, along with 592 prospective and retrospective studies, alcohol use is a leading risk factor for global disease burden and causes substantial health loss. We found that the risk of all-cause mortality, and of cancers specifically, rises with increasing levels of consumption, and the level of consumption that minimizes health loss is zero. These results suggest that alcohol control policies might need to be revised worldwide, refocusing on efforts to lower overall population-level consumption.
The authors identified individual randomized controlled trials from previous meta-analyses and additional searches, and then performed meta-analyses on cardiovascular disease outcomes and all-cause mortality. Conclusive evidence for the benefit of any supplement across all dietary backgrounds was not demonstrated; therefore, any benefits seen must be balanced against possible risks.
4). Environment & Risk Factors

AV Khera, V Fuster, PM Ridker et al., NEJM 2016; 375:2349
Most Common Combinations of Tobacco Products Among Adult Multiple-product Users

The purpose of this study was to investigate the effects of flavored e-cigarette liquids (e-liquids) and serum isolated from e-cigarette users on endothelial health and endothelial cell–dependent macrophage activation. The cytotoxicity of the e-liquids varied considerably, with the cinnamon-flavored product being most potent and leading to significantly decreased cell viability, increased reactive oxygen species (ROS) levels, caspase 3/7 activity, and impaired tube formation and migration, confirming endothelial dysfunction also validated by the serum experiments. Acute exposure to flavored e-liquids or e-cigarette use exacerbates endothelial dysfunction, which often precedes CVD.
Human-Induced Pluripotent Stem Cell-Derived Endothelial Cells & E-Cigarette Risk

WH Lee, JC Wu et. al. J Am Coll Cardiol 2019;73:2722
Association Between Duration of Smoking Cessation & Risk of Type 2 Diabetes

Association Between Duration Of Smoking Cessation And Risk Of Death From CVD And From Any Cause

The Value of Prevention Earlier in Life

Current approach
Start statin or BP medication when ≥10% 10-year ASCVD risk

Better approach
START LDL-C & BP LOWERING EARLIER

No treatment
ASCVD & HF EVENTS & DEATH
ASCVD & HF events & deaths prevented with current approach

Fundamentally altered course of atherosclerosis & cardiac dysfunction will largely reduce the population burden & cost of CVD

Additional ASCVD & HF events & deaths prevented

Disease progression & increasing burden of disease

Advancing age

SS Gidding and J Robinson. J Am Coll Cardiol 2019;74:342
From Aging / Disease to Youth / Health

2005 - 2019

Secondary
50-100 yrs

Primary
25-50 yrs

Primordial
00-25 yrs

1) DEMENTIA
2) DEMENTIA
3) LONGEVITY
4) HRP
   PESA
   AWHS
5) IIIP
   50/50
6) SHE
7) HARLEM
   NY - NIH
   VILLAGE

CABG - ASA
Imaging-MRI
PCI - Rapamycin
FREEDOM
Increasing Communications among Brain Regions over Time

JN Giedd. Scientific American 2015;312:32
Science 2019 – Brain Development
EDUCATIVE GOAL: HEALTHY HABITS FOR CHILDREN BETWEEN 3 & 5 YRS
Long-Term Results of the SI! Program in Colombia for Health Promotion in Children

6/2). SHE - SPAIN CHILDREN’S PROJECT - 2,000

J Am Coll Cardiol 2018;72:3310
**SHE CHILDREN’S PROGRAM – N=50,000**

| Pre-school & Primary Study (CCAA Madrid) |  
|----------------------------------------|---|
| C1                                      | 6 |
| C2                                      | 6 |
| C3                                      | 12 |
| 3y.o                                    |  

24 schools/2,062 children

| Primary Study (CCAA Madrid) |  
|----------------------------|---|
| C1                         | 12 |
| C2                         | 12 |
| C3                         | 12 |
| C4                         | 12 |
| 6 y.o                      |  

21 schools/469 children (who started at 3 y.o.)

| Secondary Study (CCAA Catalonia- Madrid) |  
|----------------------------------------|---|
| C1                                      | 8 |
| C2                                      | 8 |
| C3                                      | 8 |
| 12 y.o                                  |  

48 schools/1,769 children

|                               |  
|----------------------------|---|
| C1                         | 8 |
| C2                         | 8 |
| C3                         | 8 |
| 12 y.o                     |  

24 High schools / 1,200 children

**Intervention**  
**Control**  
**Pre-school**  
**Primary**  
**Secondary**
From Aging / Disease to Youth / Health

2005 - 2019

Secondary
50-100 yrs

Primary
25-50 yrs

Primordial
00-25 yrs

1) FREEDOM
2) DEMENTIA
3) LONGEVITY
4) HRP PESA AWHS
5) IIIP 50/50
6) SHE
7) HARLEM NY - NIH VILLAGE

CABG - ASA Imaging-MRI PCI- Rapamycin

Imaging-MRI
Health Promotion Among Preschoolers in Underserved Communities: The FAMILIA Trial

**Intervention**
Health promotion program

**Cluster randomization**
Head Start preschools
Children 3-5 years

**Control**
Usual curriculum

**Primary outcome**
Change in KAH score

**Absolute change in KAH score (points)**

**Schools** (n=9)
Children (n=398)

**Schools** (n=6)
Children (n=164)

KAH score
TEC
BMI z-score

KAH score
TEC
BMI z-score

KAH score
TEC
BMI z-score

KAH score
TEC
BMI z-score

PI: Valentin Fuster

N=2,500

Project I:
Validation Teachers
Project II: Exposome

→ Recruit 400 well phenotyped FAMILIA children

→ Assess metal pollutants, essential elements, and breast feeding (juvenile teeth).
→ Lipid profile (Proteomics Core)
  * Austin et al. Nature 2013*
  * Arora et al. Nature Comm 2017*
  * Austin et al. Science Adv 2017*

→ Assess air pollution and light at night

*Rosa et al. Env Int 2017*
*Kloog et al. Chronobiol 2011*

→ 570 children aged 3-5 yrs were recruited into FAMILIA from 2015-17. We have extensive phenotypic, dietary, lifestyle and genetic/genomic data on these children.
→ Juvenile teeth are shed from age 5.5 onward – making this cohort ideal for further study of the exposome as proposed.
Estimated Risk of CAD Mortality Due To Fine Particle Air Pollution In NY - 2014

Relative risk of IHD mortality attributable to PM$_{2.5}$ air pollution in NYC, 2014

M B Hadley et. al. Circulation. 2018;137:725
The Lancet Countdown on health and climate change: from 25 years of inaction to a global transformation for public health

Fine particulate matter $<2.5 \mu m$ (PM$_{2.5}$) air pollution is the most important environmental risk factor contributing to global CV mortality and disability. Short-term elevations in PM$_{2.5}$ increase the relative risk of acute CV events by 1% to 3% within a few days. Longer-term exposures over several years increase this risk by a larger magnitude ($\approx 10\%$), which is partially attributable to the development of cardiometabolic conditions (e.g., hypertension and diabetes mellitus).
Sources And Trends In Particulate Pollution

Lancet 2018; 391: 581
Mediterranean Diet and the Association of Air Pollution and CVD Mortality Risk

The NIH / AHA for RetiredPersons Diet and Health Study, a prospective cohort (N=548,845) across 6 states and 2 cities in the United States and with a follow-up period of 17 years (1995-2011), was linked to estimates of annual average exposures to fine particulate matter and nitrogen dioxide at the residential census-tract level. The alternative Mediterranean Diet Index, which uses a 9-point scale to assess conformity with a Mediterranean-style diet, was constructed for each participant. A Mediterranean diet reduced CVD mortality risk related to long-term exposure to air pollutants. Increased consumption of foods rich in antioxidant compounds may aid in reducing the disease burden associated with ambient air pollution.

CC Lim, GD Thurston et al., Circulation 2019; 139:1766 (NYU)
HR With Air Pollutants By Quintiles Of aMed (Alternative Mediterranean Diet Index) Score

CC Lim, GD Thurston et. al. Circulation. 2019;139:1766 (NYU)
Ambient air pollution is a major health risk, leading to respiratory and CV mortality. A recent Global Exposure Mortality Model, based on an unmatched number of cohort studies in many countries, estimates that air pollution reduces the mean life expectancy in Europe by about 2.2 years, with an annual, attributable per capita mortality rate of 133/100,000. Between 40% and 80% are due to CV events; the global mortality rate is estimated higher than tobacco.

J Lelieveld, T Münzel et al., Eur Heart J 2019; 40:1590
Excess Mortality Attributed To Air Pollution In Europe, and The Disease Categories

790,000 excess deaths due to ambient air pollution per year in Europe

- Lung cancer: 7%
- Pneumonia: 7%
- COPD: 6%
- Ischemic heart disease: 40%
- Other non-communicable diseases: 32%
- Stroke: 8%

Newspaper Reporting on Health & Climate Change (For 18 Newspapers), By WHO Region

Lancet 2018; 391: 581
PPG

PI: Valentin Fuster

N=2,500
Despite major strides in reducing CVD burden with modification of classic risk factors, significant residual risks remain. Recent discoveries that linked intestinal microbiota and CVD have broadened our understanding of how dietary nutrients may affect CV health and disease. Our evolving understanding of intestinal microbiota-derived physiological modulators (e.g., short-chain fatty acids) and pathogenic mediators (e.g., trimethylamine N-oxide or TAMO) of host disease susceptibility have created novel potential therapeutic opportunities to improve CV health.
1). Intestinal Microbiota & its Metabolic Contributions to CV Health and Disease

Carnitine and choline are major nutrient precursors for gut microbiota-dependent generation of the atherogenic metabolite, trimethylamine N-oxide or TMAO. We performed randomized-controlled dietary intervention studies to explore the impact of chronic dietary patterns on TMAO levels, metabolism and renal excretion. Chronic dietary red meat increases systemic TMAO levels through: (i) enhanced dietary precursors; (ii) increased microbial TMA/TMAO production from carnitine; and (iii) reduced renal TMAO excretion. Discontinuation of dietary red meat reduces plasma TMAO within 4 weeks.
Effect of A Red Meat Containing Diet on The Metaorganismal Trimethylaminen-oxide Pathway

Z Wang, SL Hazen et. al. Eur Heart J. 2019;40:583 (Cleveland Clinic)
Potential Therapeutic Targets For Reducing Plasma TMAO Levels

A Davies, TF Lüscher. Eur Heart J. 2019;40:595
7/3. CARDONA MEXICO PERU ?
The Future of Promoting Health

- Villages (3)
- Family (1)
- Adults (5)
- Children (3)

CONCEPTS, SCIENTIFIC STUDIES, NPOs
Synergistic Opportunities in the Interplay Between Cancer Screening and CVD Risk Assessment

CVD and cancer continue to be the 2 leading causes of death in developed countries. With many shared modifiable risk factors, cancer and CVD often coexist in the same individuals; those diagnosed with lung cancer, breast cancer, and colon cancer are at higher risk of CVD, and those with CVD are at higher risk of developing many types of common cancers. Screening paradigms have been established in parallel, but there are opportunities for combined risk assessments for cancer and CVD risk.

CE Handy, M Cainzos-Achirica et al., Circulation 2018; 138:727
Pathophysiological Links Between Cancer & CVD

CE Handy, M Cainzos-Achirica et al. Circulation. 2018;138:727
Opportunities For Combined Screening & Prevention

<table>
<thead>
<tr>
<th>Screening Tests</th>
<th>Information possibly obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose chest CT</td>
<td>Current: Lung cancer detection</td>
</tr>
<tr>
<td></td>
<td>Possible: CAC score for CVD risk assessment</td>
</tr>
<tr>
<td>Cardiac CT</td>
<td>Current: CAC score for CVD risk assessment</td>
</tr>
<tr>
<td></td>
<td>Possible: Lung cancer detection (with additional lung window)</td>
</tr>
<tr>
<td>Mammography</td>
<td>Current: Breast cancer detection</td>
</tr>
<tr>
<td></td>
<td>Possible: BAC assessment for CVD screening</td>
</tr>
</tbody>
</table>

B

Combined risk factors:
- Smoking
- Obesity
- Low level physical activity

Combined primordial prevention

Cancer/CVD

Shared secondary prevention:
- Personalized screening adjustment:
  - Early cancer detection informing CVD risk assessment
  - CVD risk informing cancer screening

Combined screening & risk assessment approaches CVD risk informing cancer screening

Combined primary prevention

CE Handy, M Cainzos-Achirica et al. Circulation. 2018;138:727
1). MCP Bases of Transition from Disease to Health

1. Two Critical Tools – Imaging, Genetics

2. Three Behavioral Ages - Elderly, Mid Life, Children

3. Two Historical Paths – B. Blockers, ACE / ARBs / ARNI

4. Two Historical Paths – Statins / PCSK9i, SGLT2i / GLP1-RA

Cardona, July 15, 2019

No Disclosures