Reply to Cirillo: Early-life exposure to the sugar-rationing regime, not a measured sugar dose, drives the cancer gradient

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We thank Cirillo (1) for a close reading of our paper (2) and replication package (3). The comment concerns what the exposure measures rather than the estimates. Read as effects of early-life exposure to the sugar-rationing regime, not of a measured sugar dose, our findings survive each of the four points, taken in turn below.

1. Timing. Relaxation of rationing was staged: sweets were derationed in February 1953, and the sugar ration rose from 10 to 14 oz per week on 19 April and to 16 oz on 17 May, before abolition in September (4). Household purchases also reflect summer stock-building and a post-derationing dip (4), not infant ingestion. The direct test is to re-date the cutoff: at end June or end March 1953 the gradient is intact, and the hazard ratio per six months changes by at most 0.02 for every cancer (Table 1).

2. Infant exposure. The recommended addition of sugar to National Dried Milk (6) documents a direct channel from household sugar availability to infant intake. Identification does not require infants under rationing to have consumed no added sugar; it requires the regime and its removal to have shifted sugar availability and, through such channels, infant intake. We agree that our description of infant allocations was too strong: green-book entitlements existed, initially for the mother's benefit (5), while individual consumption is unobserved. Because treatment is assigned by policy exposure rather than observed consumption (ref. 2, SI Section S5), our estimates are intention-to-treat effects.

3. Concurrent dietary changes. We reproduce the comment's Table 1 only by adding series stored in tens of grams to series in grams (3, 7). Harmonizing units reverses the fruit/vegetable change from $+8.8\%$ to -3.3% and the meat change from -4.1% to $+2.2\%$ (Table 2); the fat increase reproduces. Sugar alone accounts for over three quarters of the 100–150 kcal energy rise (ref. 2, SI Section S2). Concurrent changes confound only if they vary across cohorts in a way that could generate the exposure-duration gradient. As we note (ref. 2, SI Section S8), sugar and calories cannot be fully separated, and higher energy intake may lie on the pathway from sugar availability to later health rather than confound it.

4. Dose-response. We agree that the paper reported categorical estimates without a formal trend test. Replacing the exposure groups with a continuous measure, months of the first 1,000 days under rationing (8, 9), gives hazard ratios per six additional months from 0.74 for liver cancer to 0.92 for breast cancer, with every confidence interval excluding 1 (Table 1). Individual point estimates are not perfectly monotonic, particularly for outcomes with few events, but the trend estimates show a systematic relationship between duration under rationing and later cancer risk (departures from linearity: Table 1).

Cirillo's historical evidence clarifies the nature and timing of the exposure. Read as long-term effects of differential early-life exposure to the rationing environment rather than of a precisely measured quantity of sugar, our estimates are not materially altered by the alternative exposure definitions or concurrent dietary changes raised in the comment.

References

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Table 1: Trend tests and alternative cutoffs. Each cell is a hazard ratio (95% CI) from a Cox model that replaces the five exposure-cohort indicators of ref. 2 with one linear term: months of the first 1,000 days under rationing, expressed per six months. Pre-period indicators and covariates follow ref. 2. Columns redate the end of rationing to 26 September 1953 (published), end June 1953 (after the 17 May ration increase) or end March 1953 (after sweets derationing and the 19 April increase). The last column is a Wald test of whether the five published cohort estimates depart from a linear gradient; a large P indicates no evidence against linearity.

	HR per six months, by cutoff			Departure from
Cancer	Sep 1953	Jun 1953	Mar 1953	linearity, P
Lung	0.88 (0.83–0.94)	0.88 (0.82–0.94)	0.89 (0.82–0.97)	0.194
Liver/IHBD	0.74 (0.64–0.84)	0.72 (0.61–0.85)	0.74 (0.61–0.89)	0.021
Rectum	0.90 (0.85–0.96)	0.90 (0.84–0.96)	0.89 (0.82–0.96)	$<$0.001
Prostate	0.87 (0.84–0.89)	0.86 (0.83–0.89)	0.87 (0.84–0.89)	0.115
Breast	0.92 (0.90–0.94)	0.92 (0.90–0.95)	0.90 (0.88–0.93)	0.038

Table 2: Change in household purchases, four quarters after versus four quarters before September 1953, from the replication data (3, 7). "As reported" reproduces Cirillo's Table 1 by adding series stored in grams to series stored in tens of grams; "harmonized" rescales all series to grams per day. The components of each category are inferred from reproducing the comment's figures.

Category	As reported (1)	Harmonized
Fats (butter, margarine, lard)	$+12.6\%$	$+12.6\%$
Fruit and vegetables	$+8.8\%$	-3.3%
Dairy (milk, welfare milk, cheese)	$+0.2\%$	-1.2%
Cereals	-0.6%	-3.4%
Meat (with fish, bacon)	-4.1%	$+2.2\%$