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► **To cite this version:**

Laura Ae Hughes, P van den Brandt, R. Alexandra Goldbohm, Anton Fpm de Goeij, Adriaan P de Bruine, et al.. Childhood and adolescent energy restriction and subsequent colorectal cancer risk: results from the Netherlands Cohort Study. *International Journal of Epidemiology*, 2010, 10.1093/ije/DYQ062 . hal-00589422

HAL Id: hal-00589422

<https://hal.science/hal-00589422>

Submitted on 29 Apr 2011

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**Childhood and adolescent energy restriction and
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Journal:	<i>International Journal of Epidemiology</i>
Manuscript ID:	IJE-2009-07-0551.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	08-Jan-2010
Complete List of Authors:	Hughes, Laura; Maastricht University, Epidemiology van den Brandt, P; Maastricht University, Department of Epidemiology Goldbohm, R.; TNO Quality of Life, Prevention and Health de Goeij, Anton; Maastricht University Medical Center, Pathology de Bruine, Adriaan; Maastricht University Medical Center, Pathology van Engeland, Manon; Maastricht University Medical Center, Pathology Weijnenberg, Matty; Maastricht University, Department of Epidemiology
Key Words:	colorectal neoplasms, cohort studies, adolescence, caloric restriction, starvation

Childhood and adolescent energy restriction and subsequent colorectal cancer risk:**Results from the Netherlands Cohort Study**

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Running Title: Early life energy restriction and subsequent colorectal cancer risk

MeSH words: colorectal neoplasms, caloric restriction, starvation, adolescence, cohort studies

20 Word count (abstract+article): 4348

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3 **Abstract:**
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5 **Background:** Energy restriction during childhood and adolescence is suggested to lower
6 colorectal cancer (CRC) risk. We investigated this in the Netherlands Cohort Study.
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10 **Methods:** Information on diet and other risk factors was collected by a baseline
11 questionnaire in 1986 when cohort members were 55-69 years of age (n=120,852). Three
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15 30 indicators of early life exposure to energy restriction were assessed: father's employment
16 status during the Economic Depression (1932-40), and place of residence during World
17 War 2 years (1940-44) and the 'Hunger Winter' (1944-45); a severe famine. Using the
18 case-cohort approach, incidence rate ratios (RR) and 95% confidence intervals (CI) were
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27 35 cancers, according to the three time periods of energy restriction. After 16.3 years of
28 follow-up, 2573 cases were available for multivariate analyses.
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31 **Results:** Men who lived in a western city during the Hunger Winter and therefore
32 exposed to the highest degree of energy restriction, had a lower risk of developing CRC
33 (RR: 0.77, 95% CI: 0.63-0.94), and tumors of the proximal colon (RR: 0.68, 95% CI:
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38 40 0.49-0.94) and rectum (RR: 0.66, 95% CI: 0.47-0.92). In women, non-statistically
39 significant inverse associations were observed for tumors of the distal colon,
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60 **Conclusions:** This unique observational evidence suggests that severe energy restriction
45 during childhood and adolescence may lower CRC risk, especially in men, thus providing
insight regarding the role of energy intake during early life in CRC development.

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Cancers of the colon and rectum are the third most common type of cancer worldwide.¹ According to the World Cancer Research Fund (WCRF), there is convincing evidence that components of energy balance such as body and abdominal fatness, and factors leading to a greater adult attained height increase the risk of colorectal cancer (CRC).¹ Numerous animal studies suggest that energy restriction may lead to the development of CRC,²⁻⁶ and observational research suggests that energy restriction during childhood and adolescence may especially be protective against CRC cancer development and or mortality later in life.⁷⁻¹⁰

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For ethical and practical reasons, it is difficult to initiate a study to test the hypothesis of childhood energy restriction and future cancer risk. However, information derived from a unique situation in the Netherlands has enabled this hypothesis to be tested. During the early to mid 20th century, a large part of the Dutch population experienced three subsequent periods of impaired nutrition: the Economic Depression of 1932-40, World War 2 (WW2) (1940-44), and a severe famine: the Hunger Winter of 1944-45.

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During the Economic Depression, there was a high rate of unemployment in the Netherlands. Surveys document that while the amount of total calories available to families with an unemployed father was sufficient, they consumed fewer calories (3000 vs. 3400 kcal/day) and had less variation in their food patterns than families with an employed father. The daily menu of the unemployed families consisted primarily of boiled potatoes and some fat, and lacked cheese, meat and confectionary.^{7, 11} During WW2, food rationing was introduced and because of poor food availability in large cities, nutritional differences emerged between people living in urban versus rural areas.

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4 70 Individuals living in cities consumed fewer calories daily; the average allowance was
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6 about 1600 kcal, which was maintained with difficulty. Furthermore, urban diets
7
8 consisted of a higher percentage of carbohydrates (70% vs 65%) and a lower percentage
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10 of fat (10% vs 15%).^{7, 12} The southern part of The Netherlands was liberated from
11
12 German occupation in September 1944, whereas the western part of the country remained
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15 75 under German rule. The Hunger Winter occurred primarily in the western cities of the
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17 Netherlands as the end result of a German imposed embargo on food transport into the
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19 major Dutch cities. While the diet remained nutritionally balanced, individuals living in
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21 western urban areas experienced rationing of less than 700 kcal per day.^{13, 14} The famine
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23 was relatively short; it abruptly ended in May 1945 when the western and northern part of
24
25 the Netherlands was liberated as well.^{13, 14} This situation provides a rare opportunity to
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27 80 study the association between severe energy restriction during childhood and
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29 adolescence, and CRC risk later in life.
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34 The Netherlands Cohort Study on diet and cancer (NLCS) is comprised of
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36 individuals who were children or going through the adolescent growth spurt during the
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38 85 years spanning the Economic Depression, WW2, and the Hunger Winter. Although
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40 individual food intake data is not available for these time periods, a number of proxy
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42 measures have been collected from cohort members that reflect their exposure to energy
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44 restriction. While the association between energy restriction during childhood and colon
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46 carcinomas was studied in the NLCS at an earlier follow-up point,⁷ that study lacked the
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48 90 power to consider risk at multiple tumor sub-sites. The present study investigated the
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50 association between population based energy restriction in childhood and adolescence
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3 and the subsequent risk of total CRC, and for tumors of the proximal and distal colon,
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6 rectosigmoid, and rectum.
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8 **Methods**

9 10 95 Study population and design

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12 The NLCS is a prospective cohort study that was initiated in 1986 with the
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14 purpose of investigating the association between diet and the development of cancer. The
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16 cohort included 58,279 men and 62,573 women between the ages of 55-69 years at
17
18 baseline who completed a self-administered questionnaire on dietary habits and lifestyle,
19
20 health, and demographic information. The questionnaire requested information about the
21
22 residence(s) of cohort members, including their residence during WW2 and the winter of
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24 1944-45, and also asked for their father's employment status during the Economic
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26 Depression. Municipal registries from throughout the Netherlands were used to constitute
27
28 an efficient sampling frame.¹⁵⁻¹⁷ A case – cohort approach (12) was used for data
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30 processing and analysis; case subjects were derived from the entire cohort, and the
31
32 number of person-years at risk for the entire cohort was estimated from a subcohort of
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34 5000 men and women who were randomly sampled from the full cohort at baseline.
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36 Further details of the design of the NLCS have been described in previous publications.¹⁵⁻
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46 110 Incident CRC cases from the entire cohort were identified by annual record
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48 linkage to nine regional cancer registries and a national pathology database (PALGA).
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50 This method of record linkage has been described elsewhere.¹⁸ The completeness of
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52 cancer follow-up has been estimated to be almost 100% .¹⁹ CRCs were classified as
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54 proximal colon cancer (International Classification of Diseases for Oncology, first edition
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3 115 codes 153.0, 153.1, 153.4, 153.5 and 153.6), distal colon cancer (codes 153.2, 153.3 and
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5 153.7), rectosigmoid (code 154.0) and rectal cancer (code 154.1). All prevalent cancer
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7 cases at baseline other than non-melanoma skin cancer and subjects with incomplete or
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9 inconsistent questionnaires were excluded. After additionally excluding individuals who
10
11 were missing variables that were adjusted for in the multivariate analysis, 3981 sub-
12
13 cohort members and 2971 CRC cases (Men: 484 proximal colon, 584 distal colon, 189
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15 120 rectosigmoid, 436 rectum, 48 not classified; Women: 514 proximal colon, 372 distal
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17 colon, 95 rectosigmoid, 225 rectum, 30 not classified) were ultimately included in the
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19 analysis.
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24 25 26 Assessment of Energy Restriction

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28 125 Individual food intake data of the cohort members was not available for the three
29
30 periods of energy restriction. Therefore, proxy variables were used to describe exposure
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32 to energy restriction.
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35 With respect to the Economic Depression years, the best proxy available was the
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37 employment status of the cohort member's father during this time frame. On the baseline
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39 130 questionnaire, individuals were asked 'was your father employed during the crisis of
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41 1932-1940?' Cohort members could either answer yes, along with the years that he was
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43 employed, or no. For analyses purposes, answers were categorised into 'father was
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45 employed during the economic depression' or 'father was not employed during the
46
47 economic depression'.
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51 135 For the years spanning both WW2 and the Hunger Winter, place of residence was
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53 used to approximate the exposure to energy restriction. Place of residence in 1942
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55 (midpoint of the war years) was used as a proxy for energy restriction during WW2. On
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3 the baseline questionnaire, cohort members were asked to list the last four residences they
4 lived in, the province where these residences were located, and the years that they lived in
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9 140 these locations. The location of residence during the mid-point of WW2 was
10 dichotomised to 'lived in a city in 1942', or 'lived in a rural area in 1942'. Additionally,
11 cohort members were specifically asked where they lived during the winter of 1944-45.
12 Residing in a western city during the Hunger Winter was considered an indicator for
13 severe energy restriction. Eleven cities in the west of the Netherlands were considered
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20 145 famine cities based on the definition by Stein et al.²⁰: Amsterdam, Rotterdam, The Hague,
21 Utrecht, Zaandam, Hilversum, Amersfoort, Dordrecht, Vlaardingen/Schiedam, Delft, and
22 Leiden. Answers to this question were classified into three categories: lived in a western
23 city, lived in a western rural area, and lived in a non-western area of the Netherlands
24 during the winter of 1944-1945.
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31 150 Data Analyses

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34 Data were analysed using Stata (version 9.2, Statacorp, College Station, TX,
35 USA). Because the etiology of CRC may differ according to sex and sub-site of the
36 cancer, men and women were analysed separately for overall colorectal (including
37 rectosigmoid), colon, proximal colon, distal colon, rectosigmoid, and rectal cancers.
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44 155 Cox proportional hazard analysis using the case-cohort approach was used to
45 obtain incidence rate ratios (RR) and 95% confidence intervals (CI) for the association
46 between the three proxy measures of energy restriction and the incidence of CRC overall,
47 and for each sub-site. The proportional hazards assumption was tested using the scaled
48 Schoenfeld residuals and by visual inspection of the hazard curves. When the
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55 160 proportional hazards test appeared to be violated, analyses were done for short and long
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3 follow-up by splitting up the follow-up time at 8 years. To account for the additional
4 variance introduced by sampling the sub-cohort from the entire cohort, standard errors
5 were estimated using the robust option.
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10 RRs were estimated using age-adjusted and multivariate adjusted models.
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12 165 Potential confounders that introduced a more than 10% change in RRs or contributed
13 significantly to the prediction were included as covariates in the multivariate model.
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15 These ultimately included age, family history of CRC, height, body mass index, baseline
16 alcohol and energy intake, recreational physical activity, level of education, and smoking
17 history.⁷ RRs were expressed using ‘father was employed during the economic
18 depression’, ‘lived in a rural area in 1942’, and ‘lived in a non-western area of the
19 Netherlands during the Hunger Winter’ as the reference categories for the different
20 proxies of energy restriction.
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32 Previously in the NLCS, sub-group analysis was conducted after 7.3 years of
33 follow-up to assess if timing of exposure modified the effect of energy restriction on
34 colon carcinoma cancer risk.⁷ In that study there were too few cases in each sub-group to
35 reach definitive conclusions; therefore, we repeated this sub-group analysis in terms of
36 175 total CRC to include the maximum number of cases. For each of the three exposure
37 periods, individuals were classified into a sub-group depending on if they were exposed
38 to energy restriction before, during, or after the adolescent growth spurt. Men and women
39 were analysed separately. For men, the growth spurt was defined as occurring between
40 the ages of 12 and 15. For women, the growth spurt was defined as 2 years before the
41 reported age of menarche to 1 year after the reported year of menarche (mean age
42 Economic Depression: 13.1 years, WW2: 14.3 years, Hunger Winter: 14.8 years). The
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3 long exposure periods of the Economic Depression and WW2 years were restricted to
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6 185 those years when food shortages were reported to be the most severe: 1933-1934 and
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8 1942-1943 respectively. Therefore, only individuals who met the definition of going
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10 through their growth spurt (i.e. males who were 12-15 years of age) during 1933-34 or
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12 1942-43 were included in the sub-group. While many more CRC cases were available
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14 compared to the analysis at 7.3 years follow-up, the female sub-group 'exposed before
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17 190 growth spurt to the Hunger Winter' still had too few cases for the model to converge. Due
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19 to an extremely low number of cases, associations for women exposed to the Hunger
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21 Winter before their adolescent growth spurt are not reported.
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25 Finally, tests for heterogeneity were done to evaluate differences between
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27 subtypes of tumors (e.g., colon vs. rectum) using the competing risks procedure in
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29 195 STATA. However, the SE for the difference of the log-hazard ratios from this procedure
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31 assumes independence of both estimated hazard ratios, which would overestimate that SE
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33 and thus overestimate the *P* values for their difference. Therefore, these *P* values and the
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35 associated confidence intervals were estimated based on a bootstrapping method that was
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37 developed for the case-cohort design.²¹ Each bootstrap analysis was based on 1,000
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41 200 replications.
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43 Results

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46 Baseline characteristics of the sub-cohort are presented in **table 1** and **table 2** for
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48 men and women, respectively. Men who lived in a western rural area during the Hunger
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50 Winter had a higher level of occupational physical activity and a higher level of
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53 205 education compared to men who lived in a non-western area or a western city. With
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55 respect to the war years, men who lived in a western city in 1942 had a lower BMI and a
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3 lower daily intake of calories at baseline compared to men who did not. Additionally,
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5 these men had a higher level of education and a lower level of occupational physical
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7 activity. Men who had an employed father during the Economic Depression had a higher
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10 level of education and had a lower level of occupational physical activity than men whose
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12 father was not employed. Women who lived in a western city during the Hunger Winter
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14 had a lower energy intake and a higher intake of alcohol at baseline compared to women
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16 who lived in a non-western or western rural area, and a higher level of education. Women
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18 who lived in a western rural area had the lowest proportion of CRC family history.
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22 215 Women who lived in an urban area in 1942 were shorter, had a lower energy intake and a
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24 higher alcohol intake at baseline, had a higher level of education, exercised more, and
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26 smoked less than women who lived in a rural area. Women whose father was employed
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28 during the Economic Depression were younger, taller, had a lower BMI, a higher intake
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30 of alcohol and energy at baseline, were better educated, and smoked less than women
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34 220 whose father did not have a job.

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36 Associations between the three proxy measures of energy restriction and CRC risk
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38 are presented in **table 3** for men and **table 4** for women. Men who reported living in a
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40 western city during the winter of 1944-1945 had a lower risk of CRC compared to men
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42 who lived in a non-western area (RR 0.77, 95% CI: 0.63-0.94). With respect to tumor
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46 225 sub-site, living in a western city during the Hunger Winter was protective against risk of
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48 tumors of the total colon (RR: 0.76, 95% CI: 0.60-0.96), proximal colon (RR 0.68, 95%
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50 CI: 0.49-0.94), and rectum (RR: 0.66, 95% CI: 0.47-0.92). Living in a city in 1942 and
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52 having a father without a job during the economic depression were not associated with
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3 CRC, or the specific CRC sub-sites. Tests for heterogeneity suggest that there is no
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6 230 difference in risk between the tumor subsites.

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8 In women, living in a western city during the Hunger Winter was not associated
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10 with total CRC risk (RR: 0.99, 95% CI: 0.83-1.18). Analyses according to tumor sub-site
11
12 were heterogeneous. Living in a western city was inversely associated with tumors of the
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14 distal colon, rectosigmoid, and rectum, while an increased risk was observed for proximal
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17 235 colon tumors (RR: 1.23, 95% CI: 0.97-1.56). Residing in a city in 1942 was inversely
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19 associated with risk of rectal cancer (RR 0.69, 95%CI: 0.47-0.93), but was not associated
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21 with tumors at other sub-sites. Having a father without a job during the economic
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23 depression was not associated with CRC risk or the risk of cancer at each sub-site. Tests
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26 for heterogeneity indicate that there is no difference in risk between the tumor subsites.
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29 240 Results from the sub-group analyses can be seen in **table 5**, for both men and
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31 women. Our cohort has no men who were exposed to the Hunger Winter before their
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33 growth spurt. In men, exposure to energy restriction during or after the growth spurt was
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35 protective against CRC for those who resided in a western city during the Hunger Winter
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37 compared to those who resided in non-western area (RR: 0.56, 95% CI: 0.31-1.03 and
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40 245 RR: 0.76, 95% CI: 0.61-0.94, respectively). Residing in a western rural area during the
41
42 Hunger Winter also seemed to be protective of CRC in men as opposed to residing in a
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44 non-western area a that time (RR: 0.52, 95% CI: 0.26-1.02). In women, too few cases
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46 were exposed to the Hunger Winter before the growth spurt to reach definitive
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48 conclusions. There were no clear associations or differences between sub-groups during
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53 250 the War Years or Economic Depression for both men and women.

54 55 **Discussion** 56 57 58 59 60

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In this large prospective cohort study, we examined the association between energy restriction in childhood and adolescence and CRC risk at a number of tumor sub-sites. After 16.3 years of follow-up in the NLCS, almost 3000 CRC cases were available for analysis. In men, we observed that living in a city classified as having experienced the greatest degree of caloric rationing during the Hunger Winter²² was inversely associated with the risk of developing CRC. While inverse non-statistically significant associations were also observed in women, it appears that risk may differ according to sub-site.

Prior to discussing these results further, it is important to address an important limitation in our study. Because information on individual food for the cohort was not available for the exposure periods, three proxy measures of energy restriction were used to describe energy restriction during the Economic Depression, WW2, and the Hunger Winter. It is possible that using the father's employment status, place of residence during WW2, and place of residence during the Hunger Winter has resulted in some misclassification of exposure; however, in a follow-up study in the NLCS, female sub-cohort members were asked if they really had experienced hunger during the winter of 1944-1945. Of the women who reported severe hunger, 80% lived in a western city during this winter.²³ These results indicate that place of residence during the Hunger Winter is a reasonably adequate proxy of exposure, although unavoidable misclassification may have caused attenuation of the association. While it has been proposed that individual famine data may be more accurate than area-exposure data,²⁴ other studies in the Netherlands have used place of residence during the Hunger Winter as a measure of energy restriction,^{25, 26} and their results indicate that it is an adequate proxy.

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3 275 The strong inverse associations we observed during the period of the Hunger
4 Winter, especially for those who lived in a western city, suggest that in men, it may be
5 caloric restriction as opposed to specific nutrient restriction that modulates the risk of
6 CRC. This observation is in line with evidence from animal studies ²⁷⁻²⁹ and could
7 explain why we observed weaker, non-statistically significant associations during the
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15 280 other two periods of exposure when caloric restriction was assumed to be less severe.
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17 Alternatively, new insights reported by Trienekens et al ³⁰ suggest that while there was
18 heavy rationing in the years prior to the Hunger Winter, food distribution was generally
19 satisfactory in the Netherlands, regardless of geographical area. However, this was only
20 true up until the period of the Hunger Winter (1944-1945). It could therefore be argued
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27 285 that differences are not to be expected when using 'place of residence during the war
28 years (1940-44)' as a proxy for exposure to energy restriction as the contrast in exposures
29 is too small.
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34 In the female population, our observations were more heterogeneous. It was
35 interesting to observe that energy restriction during the Hunger Winter was inversely
36 associated with tumors of the distal colon, rectosigmoid, and rectum, but a slightly
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38 290 elevated risk was observed with tumors of the proximal colon. Also, energy restriction
39 during WW2 was significantly protective against rectal tumors, but again, positively
40 associated with tumors of the proximal colon, although not statistically significant.
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51 295 of CRC at different sub-sites. We can only speculate about why we observed differences
52 between men and women in terms of CRC risk. The majority of female cases were
53 exposed to the Hunger Winter at least one year following their first menstrual period. For
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3 women in this sub-group, circulating estrogen levels would have been much higher
4 compared to the women exposed before and during the adolescent growth spurt. It has
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9 300 been suggested that the beneficial effect of caloric restriction on CRC risk is mediated
10 through its influence on IGF (especially IGF-1).³¹ However, IGF is also influenced by
11 estrogen.³² Therefore, some interaction between these two hormones may have offset a
12 positive influence of caloric restriction, and could explain why we did not observe a
13 reduced RR for CRC in women exposed to the Hunger Winter.
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20 305 Our findings are generally consistent with other epidemiological studies. The
21 association between energy restriction in childhood and colon carcinoma risk was
22 previously investigated in the NLCS after 7.3 years of follow-up. While limited in terms
23 of size, a weak, inverse association was reported.⁷ After 16.3 years, it appears that the
24 protective association previously observed for women residing in a Western city during
25 the Hunger Winter and colon carcinoma risk has been attenuated. Stratifying our data by
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31 310 the Hunger Winter and colon carcinoma risk has been attenuated. Stratifying our data by
32 early and late follow-up time (not shown) suggests that at both early and late follow-up
33 there was an increased risk of proximal colon cancer, and a decreased risk of distal colon
34 cancer. Furthermore, the difference in risk between sub-sites becomes greater with the
35 later follow-up time. This may help explain why different RR for total colon cancer were
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43 315 observed in women at 7.3 vs. 16.3 years of follow-up, and reiterates the importance of
44 assessing risk by colorectal sub-site. As of yet, there is no clear biological explanation for
45 this observation, but as none of the RR calculated at 7.3 years of follow-up or in the
46 present study were statistically significant, it is possible that these the associations
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53 observed when only considering later follow-up are due to chance alone.
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3 320 Information pertaining to exposure to energy restriction around the time period of
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5 WW2 has also been collected in several Nordic countries. In Norway, a country that
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7 experienced a 20% reduction in energy intake during WW2, it has been observed that
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9 individuals born during or shortly after the War have a decreased risk of CRC compared
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11 to individuals who were not born around this period.⁹ It is interesting to observe that this
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13 trend extends to Estonia, but not to Finland; two countries that both experienced severe
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15 325 restriction.¹⁰ It has been proposed that the effects of caloric restriction may have been
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17 counteracted in the Finnish population because approximately 70,000-80,000 Finnish
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19 children were sent to Sweden during WW2, a country that experienced less severe
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21 rationing.¹⁰ Furthermore, observations from the Boyd Orr cohort study in the United
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23 Kingdom suggest that there is a positive association between childhood energy intake and
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25 330 adult mortality from cancer, including gastrointestinal cancers.⁸
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32 It is important to determine the mechanisms through which energy restriction in
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34 childhood is associated with a decreased risk of CRC and how this might differ by sub-
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36 site. Adult attained height is marker of an aggregated fetal and childhood experience, and
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38 335 can be considered a proxy measure for important nutritional exposures, which impact on
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40 several hormonal and metabolic axes.¹ In the present study, height was not acting as an
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42 intermediate variable in the risk between exposure to energy restriction and CRC. This
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44 was not surprising, as adult height may be most influenced early in childhood, and most
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46 individuals in our study were exposed to the Hunger Winter in the later years of
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48 340 childhood and puberty. Long term effects on insulin, insulin like growth factors
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50 (especially IGF-1), and adipokines such as leptin have also been proposed as possible
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52 mechanisms,^{4, 9, 10, 13, 29} but how exposure during childhood and adolescence translates
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3 into protection during adulthood remains elusive. The exposure time frames that we
4 considered, especially the Hunger Winter, were short-term, transient periods of energy
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6 restriction.³⁰ While not directly related to the strong one-time population starvation
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8 345 studies considered here, it has been argued that acute periods of energy restriction are
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10 dangerous for humans because it can lead to the phenomenon of weight cycling, that is,
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12 repetitive periods of weight loss and weight gain that may result in a modest acceleration
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14 of the carcinogenic response.^{33, 34} However, research also suggests that subtle nutritional
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16 stimuli at specific critical periods of development can induce persistent changes in gene
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18 350 expression and metabolism through modulation of genetic and epigenetic mechanisms.^{35,}
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³⁶ This idea is supported by the observation that being overweight during adolescence may be a more powerful predictor of CRC risk than being overweight during adulthood.³⁷

We have observed that exposure to the Hunger Winter during adolescence is
355 associated with a lower risk of developing a tumour characterized by the CpG island
36 methylator phenotype (CIMP) after 7.3 years of follow-up.³⁸ CIMP is a distinct
37 characteristic of epigenetic instability in CRC development,³⁹ and our observations
38 support the hypothesis that adolescence may be a critical period of development for
39 epigenetic changes that influence CRC risk. Evidence suggests that CIMP is highly
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44 360 prevalent in the proximal colon, and in females.³⁹ While the present study suggests a
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46 positive association between exposure to the Hunger Winter and risk of tumours at the
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48 proximal colon in women, this may be a finding of chance. Although we did not observe
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50 statistically significant differences with respect to risk at tumor sub-sites, focusing on
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52 associations between energy restriction and molecular characteristics of CRC may shed
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55 365 light on potential differences in risk
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4 In conclusion, data from this unique period of Dutch history has allowed us to
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6 obtain rare observational evidence suggesting that severe energy restriction during
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8 adolescence may lower CRC risk at a number of tumor sub-sites, especially in men.
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10 These results give further insight into the role of energy intake during this period of life
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12 in CRC development.
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18 **Key Messages:** Severe energy restriction during childhood and adolescence may lower
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20 colorectal cancer risk, especially in men. More research is warranted to establish the
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22 difference in risk between colorectal tumour sub-sites, as well as the association between
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24 energy restriction and molecular characteristics of colorectal cancer.
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29 **Funding**

30
31 This work was supported by the World Cancer Research Fund [2007/54 to M.P.W]
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33

34 **Acknowledgements**

35
36 380 We are indebted to the participants of this study and thank the cancer registries (IKA,
37
38 IKL, IKMN, IKN, IKO, IKR, IKST, IKW, IKZ, and VIKC) and the Netherlands
39
40 Nationwide Registry Pathology (PALGA). We also thank S van de Crommert and J
41
42 Nelissen for their assistance with data entry and data management; A Volovics and A
43
44 Kester for statistical advice; L Schouten, C de Zwart, M Moll, W van Dijk, M Jansen, and
45
46 A Pisters for assistance; and H van Montfort, T van Moergastel, L van den Bosch, and R
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48 385 A Schmeitz for programming assistance.
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Table 1. Distribution ^a of potential confounders according to time period of exposure to energy restriction in the male sub-cohort of the NLCS (1986) after 16.3 years of follow-up.

	Hunger Winter (1944-45) ^b			War Years (1940-44) ^b		Economic Depression (1932-40) ^b	
	Lived in Non-West	Lived in Western Rural	Lived in Western City	Lived in Rural area in 1942	Lived in Urban area in 1942	Father had a job	Father did not have a job
Number of Individuals ^c	980	249	415	729	753	1705	206
Baseline and Population Characteristics							
Age	61.1 (4.2)	60.4 (4.2)	61.0 (4.4)	61.2 (4.2)	61.5 (4.2)	61.1 (4.2)	61.6 (4.5)
Age range during period of exposure ^d	12-28 (19)	12-27 (18)	12-28 (19)	12-26 (17)	12-26 (17)	1-17 (8)	1-16 (9)
Height (m)	176.2 (6.4)	178.2 (6.8)	176.8 (6.4)	176.5 (6.6)	176.1 (6.5)	176.6 (6.6)	176.1 (6.6)
Weight (kg)	78.2 (9.2)	77.5 (9.4)	77.3 (9.3)	78.7 (9.6)	76.6 (9.2) ^e	77.8 (9.3)	77.7 (9.6)
Body Mass Index (kg/m ²)	25.1 (2.5)	24.4 (2.6)	24.7 (2.5)	25.2 (2.6)	24.7 (2.5) ^e	24.9 (2.6)	25.0 (2.6)
Alcohol Intake (g/day)	14.8 (16.5)	14.7 (16.7)	14.9 (17.6)	13.87 (15.2)	14.2 (16.6)	14.9 (16.8)	14.1 (15.6)
Energy Intake (kcal)	2194 (520)	2197 (504)	2107 (471)	2213 (524)	2112 (473) ^e	2180 (510)	2133 (506)
Family history of CRC (%)							
No	95.3	96.0	94.7	94.9	95.2	94.9	94.2
Yes	4.7	4.0	5.3	5.1	4.8	5.1	5.8
Level of Education (%)							
Low	49.0	45.4	33.7 ^e	58.0	39.9 ^e	41.9	59.7 ^e
Medium	33.1	34.9	40.2	30.9	41.8	37.4	27.2
High	17.8	19.7	26.0	11.1	18.3	20.8	13.1
Recreational Physical Activity(%)							
<30 mins/day	16.9	20.5	17.8	16.7	17.3 ^e	16.8	21.4
30-60 mins/day	32.2	33.5	27.0	33.2	28.2	31.6	28.6
60-90 mins/day	18.7	21.7	22.4	18.0	19.7	20.1	15.1
>90 mins/day	32.1	24.5	32.8	32.1	34.9	31.6	35.0
Smoking Status (%)							
Current smoker	35.6	35.3	32.8	36.5	36.5	36.1	32.0
Ex-smoker	50.8	49.8	54.2	51.7	51.5	51.1	56.8
Never smoked	13.6	14.9	13.0	11.8	12.0	12.8	11.2

^a presented as mean (standard deviation) or percentage (%) when indicated.

^b Hunger Winter: it was assumed that individuals residing in a western area of the Netherlands, especially a western urban area during the Hunger Winter would have experienced the greatest degree of energy restriction; War Years: it was assumed that individuals who resided in an urban area during the mid-point of the War would have experienced the greatest degree of energy restriction; Economic Depression: it was assumed that individuals who had an unemployed father during the Economic Depression would have experienced a higher degree of energy restriction compared to those whose father was employed.

^c subcohort members who were not missing data for the given exposure and any of the considered baseline characteristics.

^d age range (mean age)

^e analysis of variance, t-test or chi-square test: p<0.05

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Table 2. Distribution^a of potential confounders according to time period of exposure to energy restriction in the female sub-cohort of the NLCS (1986) after 16.3 years of follow-up.

	Hunger Winter (1944-45)			War Years (1940-44)		Economic Depression (1932-40)	
	Lived in Non-West	Lived in Western Rural	Lived in Western City	Lived in Rural area in 1942	Lived in Urban area in 1942	Father had a job	Father did not have a job
Number of Individuals^b	1077	286	554	700	824	1728	221
Baseline and Population Characteristics							
Age	61.2 (4.3)	61.1 (4.1)	61.4 (4.3)	61.2 (4.1)	61.4 (4.4)	61.2 (4.3)	61.7 (4.2) ^d
Age range during period of exposure ^c	12-28 (19)	12-28 (19)	12-28 (19)	10-26 (17)	10-26 (17)	1-17 (8)	1-17 (9)
Age at Menarche	13.7 (1.8)	13.6 (1.7)	13.7 (1.8)	13.7 (1.7)	13.7 (1.8)	13.7 (1.7)	13.7 (2.1)
Height (m)	165.4 (6.3)	165.6 (5.8)	165.4 (5.9)	165.4 (6.0)	165.1 (6.1) ^d	165.5 (6.0)	163.6 (6.8) ^d
Weight (kg)	68.4 (10.0)	69.2 (10.3)	68.2 (9.9)	68.7 (9.8)	68.7 (10.2)	68.2 (10.0)	68.8 (10.6)
Body Mass Index (kg/m ²)	25.0 (3.5)	25.2 (3.5)	24.9 (3.5) ^d	25.1 (3.4)	25.2 (3.5)	24.9 (3.4)	25.7 (3.9) ^d
Baseline Alcohol Intake (g/day)	5.5 (9.2)	5.4 (8.2)	6.8 (10.6) ^d	4.7 (7.8)	6.3 (10.0) ^d	6.1 (9.2)	4.5 (8.0) ^d
Baseline Energy Intake (kcal)	1709 (410)	1701 (402)	1661 (365) ^d	1710 (405)	1658 (388) ^d	1692 (395)	1666 (738) ^d
Family history of CRC (%)							
No	93.2	96.3	94.7 ^d	94.8	94.9	94.2	94.5
Yes	6.8	3.7	5.3	5.2	5.1	5.8	5.5
Level of Education (%)							
Low	59.6	59.1	44.2 ^d	70.1	46.3 ^d	52.8	70.7 ^d
Medium	32.4	30.1	44.5	23.5	44.6	37.3	24.3
High	8.0	10.8	11.2	6.5	9.1	10.0	5.1
Recreational Physical Activity(%)							
<30 mins/day	23.9	17.8	21.7 ^d	31.4	23.8 ^d	21.9	28.9
30-60 mins/day	32.1	39.0	27.2	36.3	27.3	32.1	26.6
60-90 mins/day	22.1	23.8	25.6	22.0	24.5	23.6	22.5
>90 mins/day	22.0	19.3	25.4	20.4	24.4	22.4	22.0
Smoking Status (%)							
Current smoker	20.3	15.2	24.9	23.9	17.1 ^d	19.9	31.2 ^d
Ex-smoker	18.8	21.2	23.3	23.9	14.3	21.2	18.4
Never smoked	60.9	63.6	51.8	52.2	68.9	58.9	50.5

^a presented as mean (standard deviation) or percentage (%) when indicated.
^b subcohort members who were not missing data for the given exposure and any of the considered baseline characteristics
^c age range (mean age)
^d analysis of variance, t-test or chi-square test: p<0.05

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Table 3. Age adjusted and multivariate adjusted hazard rate ratios (RR) for colorectal cancers according to three time periods of energy restriction in the male population of the Netherlands Cohort Study on diet and cancer (1986-2002).

	Hunger Winter (1944-45)			War Years (1940-44)		Economic Depression (1932-40)	
	<i>Lived in non-western area^a</i>	<i>Lived in a western rural area</i>	<i>Lived in a western city</i>	<i>Lived in a rural area in 1942^a</i>	<i>Lived in an urban area in 1942</i>	<i>Father had a job^a</i>	<i>Father did not have a job</i>
Person years at risk	13, 798	3646	5774	10,336	10,445	24, 098	2850
Total Colorectal							
<i>Number of cases</i>	905	218	314	666	654	1484	184
<i>RR^b (95% CI)</i>	1.00	0.95 (0.77-1.16)	0.83 (0.69-0.99)	1.00	0.96 (0.82-1.12)	1.00	1.03 (0.83-1.28)
<i>RR^c (95% CI)</i>	1.00	0.96 (0.78-1.19)	0.81 (0.68-0.98)	1.00	0.95 (0.81-1.12)	1.00	0.92 (0.72-1.18)
Proximal Colon							
<i>Number of cases</i>	255	67	78	201	169	422	45
<i>RR^b (95% CI)</i>	1.00	1.04 (0.77-1.41)	0.73 (0.55-0.97)	1.00	0.82 (0.65-1.03)	1.00	0.88 (0.62-1.24)
<i>RR^c (95% CI)</i>	1.00	1.03 (0.76-1.41)	0.72 (0.54-0.96)	1.00	0.78 (0.61-1.00)	1.00	0.79 (0.53-1.18)
Distal Colon							
<i>Number of cases</i>	297	68	118	195	226	502	63
<i>RR^b (95% CI)</i>	1.00	0.90 (0.66-1.22)	0.95 (0.74-1.21)	1.00	1.13 (0.91-1.41)	1.00	1.04 (0.77-1.41)
<i>RR^c (95% CI)</i>	1.00	0.92 (0.67-1.26)	0.89 (0.69-1.15)	1.00	1.07 (0.84-1.36)	1.00	0.95 (0.66-1.37)
Rectosigmoid							
<i>Number of cases</i>	87	30	31	76	63	153	21
<i>RR^b (95% CI)</i>	1.00	1.35 (0.87-2.10)	0.85 (0.55-1.30)	1.00	0.81 (0.57-1.15)	1.00	1.14 (0.71-1.84)
<i>RR^c (95% CI)</i>	1.00	1.46 (0.92-2.32)	0.85 (0.55-1.31)	1.00	0.82 (0.58-1.17)	1.00	1.12 (0.65-1.95)
Rectum							
<i>Number of cases</i>	247	50	71	186	169	369	49
<i>RR^b (95% CI)</i>	1.00	0.78 (0.56-1.10)	0.69 (0.51-0.92)	1.00	0.89 (0.71-1.13)	1.00	1.11 (0.80-1.55)
<i>RR^c (95% CI)</i>	1.00	0.81 (0.57-1.15)	0.71 (0.43-0.96)	1.00	0.95 (0.74-1.23)	1.00	0.94 (0.64-1.38)

^a reference category

^b model adjusted for age

^c model adjusted for age, family history of colorectal cancer, BMI (kg/m²), energy intake at baseline (kcal/day), alcohol intake at baseline (g/day), recreational physical activity (min/day), level of education, and smoking status (yes, ex, never)

Table 4. Age adjusted and multivariate adjusted RR for colorectal cancers according to three time periods of energy restriction in the female population of the Netherlands Cohort Study on diet and cancer (1986-2002).

	Hunger Winter (1944-45)			War Years (1940-44)		Economic Depression (1932-40)	
	<i>Lived in a non-western area^a</i>	<i>Lived in a western rural area</i>	<i>Lived in a western city</i>	<i>Lived in a rural area in 1942^a</i>	<i>Lived in an urban area in 1942</i>	<i>Father had a job^a</i>	<i>Father did not have a job</i>
Person years at risk	16,070	4217	8117	10,425	3234	25,576	3234
Total Colorectal							
<i>Number of cases</i>	658	178	327	451	497	1040	124
<i>RR^b (95% CI)</i>	1.00	1.05 (0.84-1.30)	0.98 (0.82-1.16)	1.00	0.94 (0.80-1.11)	1.00	0.90 (0.71-1.14)
<i>RR^c (95% CI)</i>	1.00	1.08 (0.87-1.35)	0.99 (0.83-1.18)	1.00	0.94 (0.78-1.13)	1.00	0.91 (0.71-1.16)
Proximal Colon							
<i>Number of cases</i>	254	75	157	176	237	442	54
<i>RR^b (95% CI)</i>	1.00	1.15 (0.86-1.55)	1.21 (0.97-1.52)	1.00	1.14 (0.91-1.43)	1.00	0.94 (0.68-1.29)
<i>RR^c (95% CI)</i>	1.00	1.20 (0.89-1.63)	1.23 (0.97-1.56)	1.00	1.15 (0.90-1.47)	1.00	0.90 (0.65-1.26)
Distal Colon							
<i>Number of cases</i>	209	55	90	140	140	319	37
<i>RR^b (95% CI)</i>	1.00	1.02 (0.73-1.41)	0.85 (0.65-1.11)	1.00	0.86 (0.66-1.11)	1.00	0.90 (0.63-1.31)
<i>RR^c (95% CI)</i>	1.00	1.05 (0.75-1.48)	0.87 (0.66-1.15)	1.00	0.87 (0.66-1.15)	1.00	0.92 (0.63-1.34)
Rectosigmoid							
<i>Number of cases</i>	54	12	20	37	31	85	7
<i>RR^b (95% CI)</i>	1.00	0.86 (0.45-1.62)	0.73 (0.43-1.22)	1.00	0.71 (0.44-1.16)	1.00	0.63 (0.29-1.39)
<i>RR^c (95% CI)</i>	1.00	0.86 (0.44-1.67)	0.67 (0.39-1.17)	1.00	0.71 (0.40-1.24)	1.00	0.63 (0.28-1.41)
Rectum							
<i>Number of cases</i>	121	31	53	92	74	194	22
<i>RR^b (95% CI)</i>	1.00	0.96 (0.64-1.46)	0.84 (0.60-1.18)	1.00	0.69 (0.50-0.96)	1.00	0.88 (0.55-1.41)
<i>RR^c (95% CI)</i>	1.00	0.99 (0.65-1.54)	0.85 (0.61-1.20)	1.00	0.66 (0.47-0.94)	1.00	0.90 (0.56-1.45)

^a reference category

^b model adjusted for age

^c model adjusted for age, family history of colorectal cancer, BMI (kg/m²), energy intake at baseline (kcal/day), alcohol intake at baseline (g/day), recreational physical activity (minutes/day), level of education, and smoking status (yes, ex, never)

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Table 5. RR of CRC for men and women in the NLCS (1986-2002) exposed to energy restriction before, during, and after the adolescent growth spurt ^a, according to three different time periods of energy restriction

Exposure	Before Growth Spurt			During Growth Spurt			After Growth Spurt		
	# cases	Person years at risk	RR ^b (95% CI)	# cases	Person years at risk	RR ^b (95% CI)	# cases	Person years at risk	RR ^b (95% CI)
MEN									
Hunger Winter									
Lived in a non-west area ^c				87	2383	1.00	594	9796	1.00
Lived in western rural area	No males exposed before growth spurt			16	819	0.52 (0.26-1.02)	145	2468	1.01 (0.78-1.30)
Lived in western city				21	1042	0.56 (0.31-1.03)	208	4327	0.76 (0.61-0.94)
War Years									
Lived in a rural area in 1942 ^c	25	836	1.00 ^{d,e}	90	2329	1.00	371	6014	1.00
Lived in a city in 1942	24	795	0.91 (0.37-2.26)	92	2492	1.03 (0.68-1.55)	377	6480	0.85 (0.69-1.05)
Economic Depression									
Father had a job ^c	783	16710	1.00	217	3546	1.00	113	1484	1.00
Father had no job	92	1888	0.98 (0.73-1.31)	24	430	0.94 (0.51-1.70)	15	275	0.89 (0.34-2.29)
WOMEN									
Hunger Winter									
Lived in non-west area	15	390	--- ^d	88	3511	1.00	538	12169	1.00
Lived in western rural area	1	81	---	21	1017	0.87 (0.50-1.53)	151	3119	1.14 (0.89-1.46)
Lived in a western city	2	232	---	41	1840	0.89 (0.57-1.39)	277	6045	1.08 (0.89-1.32)
War Years									
Lived in a rural area in 1942	28	1093	1.00	81	2701	1.00	336	6657	1.00
Lived in city in 1942	32	1398	0.68 (0.30-1.53)	97	951	1.01 (0.66-1.54)	353	7560	0.94 (0.76-1.18)
Economic Depression									
Father had a job	644	18290	1.00	296	5156	1.00	100	2131	1.00
Father had no job	73	2189	0.90 (0.66-1.23)	30	659	0.77 (0.46-1.29)	17	385	0.92 (0.43-1.97)

^a age of growth spurt defined as: Men (12-15 years old), Women (2 years before reported age of menarche – 1 year after reported age of menarche)

^b RR adjusted for age, family history of CRC, BMI, baseline alcohol intake, baseline energy intake, baseline recreational (women) or occupational (men) physical activity, level of education, and smoking status.

^c reference category

^d too few cases for model to converge

^e only age-adjusted model considered