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Modern perspective of the Rice Diet for hypertension and other metabolic diseases

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ABSTRACT

Background In the early 1940s, before antihypertensive drugs were available, the Rice Diet Programme (RDP) was developed to treat severe hypertension and, later, diabetes and obesity. Despite significant advancements in dietary management for these conditions since then, debates remain regarding the proper guidelines for sodium and macronutrients intakes. The patient care records of RDP offer a unique source of longitudinal examination of a very low sodium (<10 mmol/day), fat, cholesterol and protein diet on blood pressure (BP), other health markers and survival.

Methods In 2019, the Rice Diet Database Project (RDDP) digitised handwritten patient care records and retinal photographs of 17 487 RDP participants, establishing a digital database for analyses. Manual transcription accuracy exceeded 97%. We used regression models to investigate the impact of dietary adherence on systolic BP (SBP) and body weight. Further, we performed Kaplan-Meier survival analysis to compare 5-year survival probability of participants defined by baseline level of SBP.

Results The database encompasses a wide array of health markers, including BP, weight, urine chloride (UCl) concentration and retinal features that offer a unique resource for studying the impact of the RDP on hypertension, diabetes and obesity. Initial analysis shows reductions in BP and weight as well as improved survival in participants with severe hypertension, underscoring the effectiveness of the diet. The data also permit examining the safety of extreme dietary sodium reduction.

The database has numerous strengths (large patient population; extensive, long-term measurements and the use of UCl excretion to document dietary adherence) and limitations (missing data; temporal changes in methodologies over 50 years and lack of control subjects).

Conclusion The RDDP database allows exploration of the effects of a diet extremely low in sodium, protein, fat and cholesterol on health indicators and patient survival. This report highlights the database's potential for detailed and intricate future analyses.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Blood pressure-lowering benefit of the extremely low-sodium Rice Diet has been shown previously in case reports and small case series.

WHAT THIS STUDY ADDS

⇒ Longitudinal data, of a large group of patients (N=17 487), demonstrating the concept of 'food as medicine' with the impact of an extremely low-sodium intervention on various health indicators including blood pressures, retinal changes and survival.

⇒ Longitudinal data of a large group of patients with malignant hypertension.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The Rice Diet Database Project (RDDP) provides data supporting sodium restriction for hypertension.

⇒ The RDDP provides clinical data and retina photos for quantitative research on the impact of the Rice Diet on longitudinal changes in retinal features.

INTRODUCTION

Effective drug therapy for hypertension was not available until the introduction of thiazide diuretics in 1958. Before that, individuals with the most severe hypertension (malignant hypertension) faced a poor prognosis (median survivals of 6 and 18 months for class IV and class III hypertension, respectively).[1] Around 1940, Kempner developed the Rice Diet, an extremely low-sodium (<10 mmol/day or <230 mg/day) regimen, to treat severe arterial hypertension, demonstrating improved health and survival in some treated patients.[2]

As medications for hypertension became available after 1958, the focus of the Rice Diet Programme (RDP) shifted to treating obesity, heart failure, kidney dysfunction and diabetes. While the RDP gained international recognition and attracted many patients from outside of the USA, there is limited evidence of its formal implementation abroad. During the RDP, patients' responses to the diet were carefully recorded on purpose-designed flowsheet charts, with urine chloride (UCl)—and later, sodium, when measurable—used to monitor adherence due to the low salt content. These paper charts, preserved in the Duke University Medical Center Archives, contain valuable information on RDP treatment of severe hypertension and other diseases.

To enable detailed analyses of the complete collection of the RDP data, the paper records were transcribed into a digital format, resulting in a database comprising information from 17 487 participants. The digitised dataset is significantly larger than previously reported in case reports or smaller patient series. Here, we describe the digitisation process and provide a first-look analysis of the effects of this unique dietary intervention programme on health outcomes.

METHODS

The RDP and participants

The RDP was primarily a residential treatment programme, where participants were hospitalised at Duke University Hospital or stayed in commercial lodgings while eating at dedicated RDP facilities in Durham, North Carolina, USA. Most participants with hypertension were referred to the RDP, while many with obesity were self-referred. There were no restrictions for admission to the RDP. As it was a patient care programme, informed consent was not required. Participants were free to leave the programme and re-enter the programme at any time, though a fee was required for participation. Those requiring inpatient hospital care were transferred to Duke University Hospital from residential care facilities. On discharge, participants often re-entered to residential care. Participants came from within and outside the USA and were enrolled for various lengths of time to treat their medical conditions. During their time in the RDP, medications were minimised or discontinued for many participants; often, the Rice Diet was the only treatment. Within the first month of participating in the RDP, about 5.7% of all participants were taking blood pressure (BP) medications. This proportion decreased to 3.3% during the second month and remained at around 2% or lower for many subsequent months. Descriptions of the RDP have been published previously.[3–6]

During their participation in the RDP, patient data were collected on handwritten charts, which were later archived at Duke University Medical Center. Participants underwent longitudinal measurements of clinical and biological markers including weight, BP, serum and urine biochemical variables, and other exams.[5] Often, biweekly 24-hour urine samples were collected and analysed for UCl concentration, a surrogate measure of urinary sodium, to monitor dietary adherence.

Many participants also had serial retinal photographs taken (N=55 332 images, see online supplemental figure 1), with retinal features (haemorrhages, exudates and papilledema) labelled by an ophthalmologist. Anteroposterior chest radiographs, ECGs, cardiac fluorograms and abdominopelvic radiographs were frequently performed. Overall, more than 110 health markers were recorded in the charts, although not all markers were measured for every patient.

The Rice Diet

The 'strict' Rice Diet provided ~150–200 mg (5–9 mmol) of sodium and 2000 kcal/day (800–1000 kcal/day for obese participants), of which ~92% were as carbohydrate, 4%–5% (<20 g/day) as protein and 2%–3% as fat.[7] The diet consisted of boiled white rice, fruit, fruit juices, multivitamins, iron (and sugar when additional calories were needed to maintain weight). If improved health conditions permitted, small amounts of potato, cereals, vegetables and meat were sometimes added. A typical meal included 1–2 cup of plain white rice, 1–2 cup of fresh fruit and fruit juice.[5]

After being treated in the RDP, participants followed the rice diet at home and returned to Durham for regular checkups. Participants often sent samples of 24-hour urine from home for UCl analysis. Many returned for residential treatment multiple times.

The Rice Diet Database Project

In 2019, the Rice Diet Database Project began digitising the paper charts and retinal photographs. The digitised data enable the analysis of the impact of the RDP on BP, weight and metabolic markers and will be available to other researchers on written request. The following sections describe the digitisation process and data quality control approaches, with examples of statistical analyses to illustrate the potential use of this database. This project was made possible through the generous gifts of anonymous donors to Duke Nephrology.

Digitisation of archived charts

The paper charts and retina images were scanned with high-resolution optical scanners (300 dpi colour TIFF for charts and at 8000 dpi for retina images) by Crowley Company (Frederick, Maryland, USA). Data from the scanned charts were then manually transcribed by iMerit Inc. (Los Gatos, California, USA) into a REDCap database maintained at Duke University Medical Center. The process of manual data entry took place over 16 months (August 2020 to November 2021) using a team of 50 staff who were trained in manual data entry using similar medical records. All data entry was monitored and checked by the project supervisor. In addition, independent staff checked the accuracy of every entry for five key variables (body weight, systolic and diastolic BP (SBP, DBP), urinary sodium and chloride concentrations). The overall accuracy of manual data entry was >97%.

Data quality control

Once manual data entry was completed, we used frequency distribution statistics to identify outliers deviating from known clinical ranges, allowing us to rectify occasional discrepancies. We also identified and corrected errors made during the initial documentation in the source charts; whenever unusable or uncorrectable (as judged by two physicians and a nutrition scientist) data were detected, they were left in the database but denoted as not suitable for analysis. The final dataset consists records from 17 487 participants. A list of available variables for analysis and their aggregate number of data points over 10 years is shown in online supplemental table 1. The number of temporally contiguous data points for individual patients from baseline across 10 years is shown in online supplemental table 2.

Automated data quality check of the manually transcribed data

In addition to a manual quality check of the transcribed data, we developed a computer vision pipeline to digitise paper sheets for comparison. Various computer vision techniques were combined to extract columns and rows, and a classifier identified different sheet formats used in the RDP. Key columns containing hand-recorded values (eg, BP, weight, UCl, urine sodium and urine potassium) were extracted using optical character recognition (OCR), with the model trained on manually labelled data. On a separate holdout test set of 1500 sheets, the OCR-derived data matched the manually transcribed data in 97.6% of cells, suggesting correct transcription, assuming no systematic errors were learnt by the OCR during the manual transcription. We further manually checked 1000 cells where the OCR-predicted and manually transcribed data matched, confirming no matching errors. Additionally, we manually reviewed 180 cells where OCR-predicted and manually transcribed data differed. We found that manual transcription errors occurred in about 25% of these cases, and OCR failed to detect 1.8% (accounting for 75% of the 2.4% discrepancy between OCR and transcribed data) of accurately transcribed cells. This indicates a manual labelling accuracy of over 99%.

Data processing and analyses

We used multivariate regression and Kaplan-Meier survival analyses to assess the association between dietary compliance to the RDP with SBP, and between baseline SBP and survival. Patient charts often spanned several years and contained variable data density. To address this, data were segmented into episodes of continuous residence, which were considered to have ended when charts showed neither BP nor weight entries for over 5 days. The initial episode for each patient was given particular focus, as it was typically the longest and marked the start of the RDP treatment. In this report, we define the baseline period as the first 5 days of the first episode for patients who stayed in the programme for at least five contiguous days (15 344 out of the total available of 17 487 participants).

Baseline SBP and DBP were defined as the mean of all measurements during this period. We categorised participants as follows: (1) severe hypertension (SBP≥180 mm Hg), (2) stages 1 and 2 hypertension (SBP ≥130 and <180 mm Hg), (3) elevated BP (SBP ≥120 and <130 mm Hg) and (4) normal BP (SBP<120 mm Hg). BP medication was used rarely, and any effects were not analysed in this report.

Baseline values for body mass index (BMI), UCl, blood urea nitrogen concentration (BUN) and urinary excretion of injected phenolsulfonphthalein were established using the first recorded value. Baseline obesity was defined as BMI ≥30 kg/m^2. Outcome BP, BMI and UCl were determined by averaging the

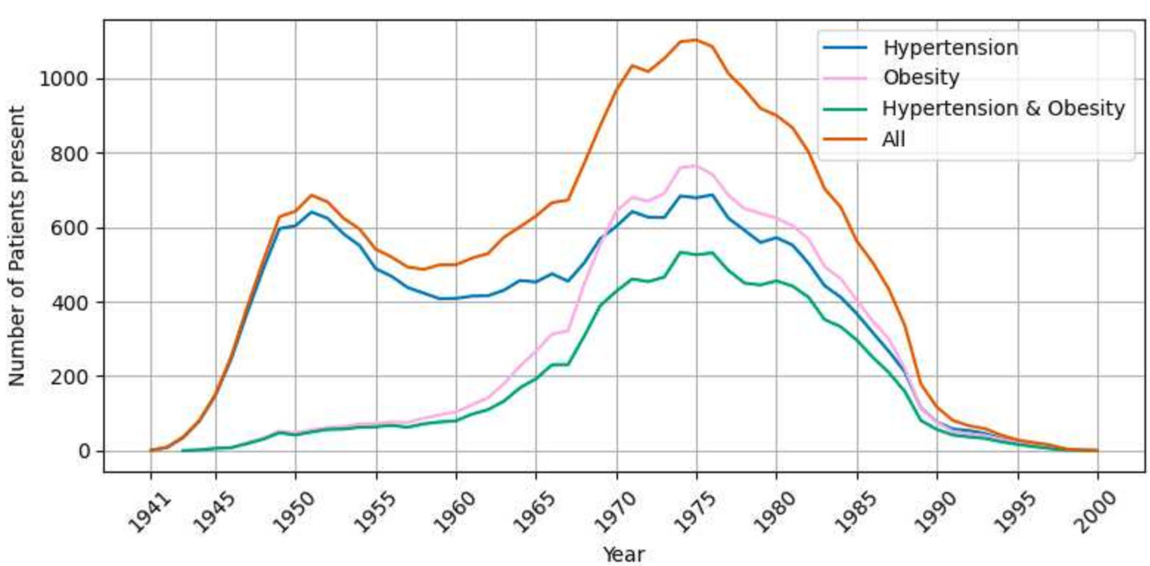

Figure 1 Number of all participants and those with hypertension or obesity enrolled by year. Numbers with hypertension or obesity are not mutually exclusive.

last three recorded values within the final 10 days of the first episode.

Multivariable linear regression modelling was used to evaluate potential predictors affecting SBP in participants with severe hypertension (SBP ≥180 mm Hg) at baseline. The average of the last three SBP measurements was regressed on baseline SBP, BMI, log-BUN, age at entry, length of participation and successful reduction of UCl below 3.5 mEq/L (consistent with a dietary intake of 5 mmol of sodium per day). Only the 1257 participants with severe hypertension and complete data for all predictors were analysed.

All analyses and plots were generated using the Python packages matplotlib, statsmodels and lifelines. Kaplan-Meier survival analysis with the log-rank test was performed to assess differences in 5-year survival of participants among different levels of SBP. Patients without a known date of death were censored at the date of their last follow-up. A $p<0.05$ is considered significant. Descriptive data are presented as medians and IQR or percentages.

RESULTS

Overall, 15 344 participants stayed in the programme for at least five consecutive days, with a median follow-up time of 162 days (IQR: 60–724). The majority (95%) were enrolled between 1946 and 1987 (figure 1), and the median age at enrolment was 48 years (IQR: 32–57) (table 1).

Among all participants, 2119 (13.8%) had severe hypertension, 6957 (45.3%) had stages 1 and 2 hypertension, 2704 (17.6%) had elevated SBP and 3564 (23.2%) had normal SBP. Those with severe hypertension were more likely to have enrolled earlier (1947–1969), were predominantly male (56.9%), older (median age: 53 years (47–60)) and stayed in the RDP longer (median: 89 days (40–114)) than those with normal SBP. A total of 14 159 participants had height data for BMI calculation, with a median BMI of 32.1 (IQR: 27.1–38.1); 15.4% had normal weight, 24.1% were overweight and 60.5% were obese.

Participants with severe hypertension had a lower median BMI (26.0 vs 29.8 for SBP<120 mm Hg) and slightly lower baseline median UCl (58.2 vs 71.9); baseline UCl did not differ significantly among other BP groups.

Table 1 Baseline characteristics of the participants by blood pressure categories

	Baseline SBP categories, mm Hg				
	<120	**120–129**	**130–179**	**≥180**	**All**
N	3564	2704	6957	2119	15 344
Male	576 (16.2%)	743 (27.5%)	2807 (40.4%)	1202 (56.9%)	5328 (34.8%)
Enrolment year*	1974 (1969–1980)	1974 (1969–1979)	1972 (1966–1978)	1950 (1947–1955)	1972 (1963–1978)
Enrolment age, years*	33 (22–47)	42 (26–53)	52 (41–61)	53 (47–60)	48 (32–57)
Length of first episode, days*†	42 (23–70)	46 (26–77)	54 (29–93)	89 (40–114)	52 (28–91)
Days until last follow-up*	344 (105–1396)	169 (63–777)	134 (57–484)	118 (48–430)	162 (60–724)
Baseline physiological markers					
Weight, kg*	80.1 (70.3–92.1)	91.2 (78.9–106.1)	96.4 (79.8–117.5)	74.4 (64.8–89.0)	88.0 (74.0–106.6)
BMI, kg/m^2*	29.8 (26.3–33.7)	33.0 (29.0–37.6)	34.9 (29.1–41.3)	26.0 (23.1–31.5)	32.1 (27.1–38.1)
Obese, %	1651 (48.0%)	1816 (69.5%)	4651 (71.6%)	454 (28.3%)	8572 (60.5%)
SBP, mm Hg*	112.5 (107.6–116.0)	124.0 (122.2–126.7)	145.5 (136.7–158.0)	204.0 (190.0–220.0)	135.0 (120.0–158.4)
DBP, mm Hg*	72.0 (67.7–76.5)	79.3 (75.3–82.0)	87.3 (82.0–94.4)	118.0 (106.7–129.9)	82.8 (76.0–94.0)
UCl, mEq/L*	71.9 (37.3–112.9)	82.1 (43.5–121.5)	77.0 (41.1–117.4)	58.2 (27.0–85.6)	75.3 (38.5–114.3)
BUN, mg/dL*	14.0 (11.0–16.0)	14.0 (12.0–17.0)	15.0 (12.0–18.0)	16.0 (12.6–21.1)	15.0 (12.0–18.0)

*Median (IQR).
†An episode is defined as a period comprising continuous measurements; it ends when neither blood pressure nor weight is recorded for over 5 days.
BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; SBP, systolic blood pressure; UCl, urine chloride.

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Table 2 Changes in selected markers from baseline to end of RDP participation

	Baseline SBP categories, mm Hg				
	<120	**120–129**	**130–179**	**≥180**	**All**
N	3564	2704	6957	2119	15 344
Survival after enrolment, years*	29.8 (19.8,38.1) N: 744	28.8 (19.4,36.6) N: 801	23.1 (13.1,31.8) N: 2534	4.5 (1.1,13.5) N: 684	23.2 (10.9,33.1) N: 4763
Lifespan, years*	76.5 (64.5,84.9) N: 734	76.6 (66.0,85.1) N: 798	76.2 (66.0,84.1) N: 2502	60.3 (51.4,70.7) N: 653	74.6 (63.0,83.6) N: 4687
Change in BMI*, kg/m^2	–3.5 (-5.4,–2.0) N: 3416	–4.3 (–6.5,–2.5) N: 2597	–4.6 (–7.3,–2.6) N: 6353	–2.8 (–4.8,–1.6) N: 1303	–4.0 (–6.5,–2.3) N: 13 669
Change in SBP*, mmHg	–3.3 (–9.2,2.5) N: 3560	–8.3 (–14.7,–2.0) N: 2699	–17.8 (–28.0,–8.3) N: 6953	–45.4 (–63.7,–27.1) N: 2119	–12.7 (–25.5,–3.3) N: 15 331
Change in DBP*, mmHg	–2.3 (–7.1,2.7) N: 3560	–4.7 (–10.0,0.0) N: 2699	–8.0 (–14.5,–2.7) N: 6953	–19.7 (–30.0,–10.0) N: 2119	–6.7 (–13.8,–0.7) N: 15 331
Change in UCl*, mEq/L	–53.6 (–20.1,–95.0) N: 2763	–62.3 (–26.2,–102.7) N: 2089	–60.5 (–24.1,–100.3) N: 5643	–48.9 (–17.8,–81.6) N: 1297	–58.1 (–22.5,–95.7) N: 11 792

*Median (IQR). N represents number in group.
BMI, body mass index; DBP, diastolic blood pressure; RDP, Rice Diet Programme; SBP, systolic blood pressure; UCl, urine chloride.

Enrolment of hypertensive participants was consistent from the late 1940s to early 1980s, while enrolment for obesity treatment increased in the early 1960s (figure 1).

All groups showed significant decreases in BMI and BP during the programme, with high dietary adherence (table 2). By the end of the RDP, median weight, BP and UCl were reduced across all groups. Median survival after enrolment in the RDP was estimated at 4.5, 23.1, 28.8 and 29.8 years for participants with severe hypertension, stages 1 and 2 hypertension, elevated SBP and normal SBP, respectively.

Dietary adherence

At baseline, the median UCl concentration was 75.3 mEq/L (38.5–114.3), implying a sodium excretion of 48.8 mmol/L (24.9–74.1). Assuming a median urine volume of 1.5 L/day and that urinary sodium excretion represents 93% of dietary intake,[8] these data suggest a baseline median sodium intake of about 1810 mg/day, much lower than anticipated.[9] We suspect many patients had already begun sodium-restricted diets before enrolling in the RDP, accounting for the relatively low baseline UCl excretion. By the end of RDP participation, UCl had decreased to a median of 5.8 mEq/L (2.8–14.3), a nearly 13-fold reduction. The UCl values of the entire cohort (data not shown) decreased with a narrow IQR (width <7.6 mEq/L after the first 14 days). Compared with anticipated chloride excretion with ~10 mEq/day ingestion, the median UCl excess was only 2.3 mEq/L per day for participants with severe hypertension and 3.9 mEq/L for other participants, indicating high dietary adherence.

Blood pressure

Most participants with severe hypertension experienced a significant BP reduction (figure 2A). Their median SBP decreased from 205 mm Hg on day 0 to 143 mm Hg on day 100 and then stabilised. As shown in table 2, participants with severe hypertension reduced their SBP by a median of 45.4 mm Hg (27.1–63.7). Regression analysis achieved an R^2 score of 0.369 for this group, with length of participation being a key factor associated with BP reduction (beta (95% CI)=–0.15 (–0.18, –0.12), p=0.000). Despite generally high adherence, only 49% of the participants achieved UCl values below 3.45 mEq/L; the median outcome SBP in the highly adherent group was 14.6 mm Hg lower than in those with higher UCl. The regression model showed that dietary adherence was significantly associated with BP decrease (beta (95% CI)=–8.9 (–11.4, –6.3), p=0.0001).

Weight loss

Because weight loss was a common outcome of RDP, even when it was not the primary goal, many severely obese participants joined the programme specifically to lose weight. figure 2B shows the weight change of all participants with an initial BMI ≥30 kg/m^2 and complete data (N=7706). The median weight decreased exponentially from 103 kg on day 0 to 80 kg on day 100. The median (IQR) weight loss in these obese participants was 14.5% (9.5%–20.7%) of their baseline weight after a median of 55 (32–87) days. We modelled outcome weight (kg) using baseline weight, length of participation and average UCl excess. All variables were significant (min p=0.000).

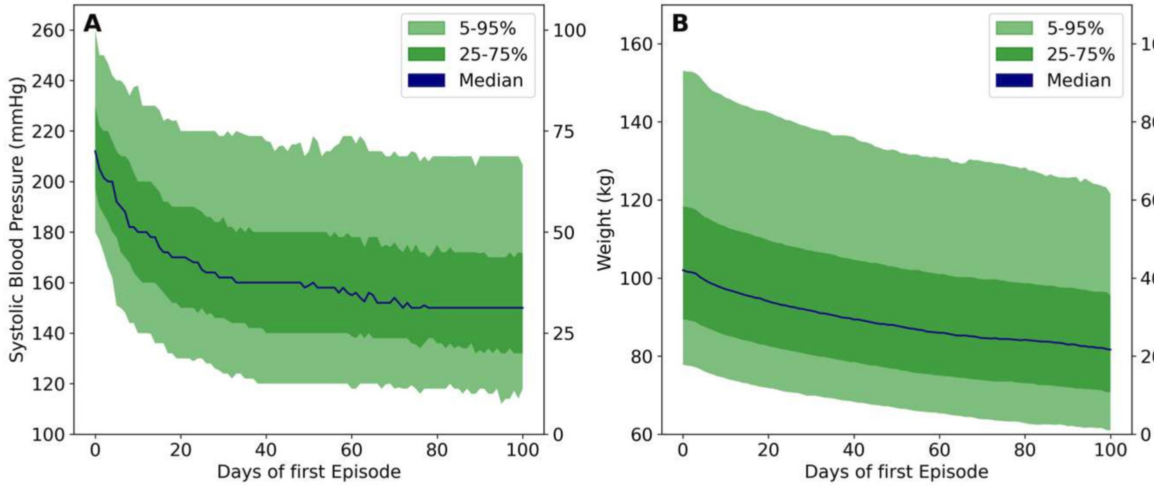
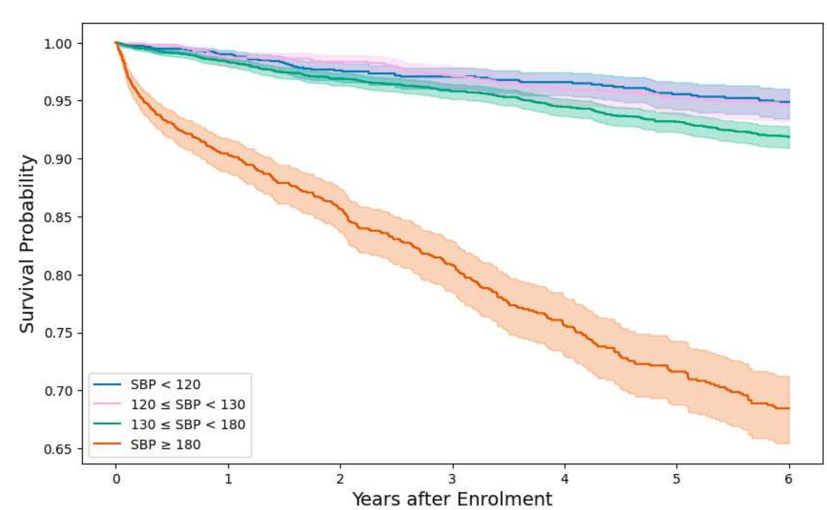


Figure 2 Response to Rice Diet treatment over time in (A) SBP for patients with severe hypertension and (B) body weight for patients with obesity.

Particularly, length of participation showed a significant effect on weight loss (beta (95% CI) = −0.165 (−0.167, 0.162), implying an average weight loss of 165 g/day or 1.2 kg/week.

Survival

Survival in the four BP groups (figure 3) was lowest for those with severe hypertension. The survival probability in this group 5 years after RDP enrolment was 71.62%, which was significantly different from the other three SBP groups: 95.55% for SBP<120 mm Hg, 95.26% for 120≤SBP<130 mm Hg, and 93.17% for 130≤SBP<180 mm Hg. The log-rank test showed significant differences between all groups except between the SBP<120 mm Hg and 120≤SBP<130 mm Hg groups. The largest difference in survival was between patients with SBP≥180 mm Hg and those below this threshold.



Number at risk by year after enrollment in RDP

Year	0	1	2	3	4	5
SBP ≥180	1980	1117	887	742	636	541
130≤ SBP <180	6682	3849	3352	3094	2902	2755
120≤ SBP <130	2585	1243	1076	999	937	886
SBP <120	3460	1420	1154	1039	968	893

Figure 3 Survival probability of the RDP participants by BP groups. BP, blood pressure; SBP, systolic BP; RDP, Rice Diet Programme.

DISCUSSION

Before the development of effective drug therapy for hypertension in 1958,[10] the RDP was an effective treatment for hypertension and diabetes. However, the exact mechanisms by which the RDP reduced BP and treated many patients with malignant hypertension remain unclear. We digitised valuable data from handwritten RDP records and created a database to examine the long-term impact of this dietary intervention on BP, weight, metabolic markers and survival. Our initial analysis revives the understanding of the RDP's benefits on the health outcomes for individuals with hypertension, obesity and diabetes.

The preliminary exploration presented in this report shows that, as expected, survival probability was lowest among patients with severe hypertension. Many early participants had malignant hypertension (severe hypertension accompanied by retinal haemorrhage, papilloedema or both); median survival for untreated malignant hypertension was 6–18 months.[1 11] However, survival improved dramatically once effective BP medications became available.[12] A detailed examination of the cohort of participants with malignant hypertension is in progress. Even among patients with 'normal' BP at baseline, the Rice Diet reduced SBP by a median of 3.3 mm Hg and DBP by 2.3 mm Hg. Other studies of dietary sodium reduction, especially the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial, have provided rigorous evidence of the diet's effectiveness in lowering BP, yet none have restricted sodium intake to the level achieved by RDP participants.[13] Some critics have questioned the safety of reducing dietary sodium intake below the recommended level of 2300 mg/day.[14] However, the RDP data suggest that extreme sodium reduction is safe, even for those with normal BP, whose 5-year survival probability was 95.6%. We acknowledge that the mortality outcomes could not be solely attributed to the impact of the diet programme. This preliminary conclusion needs further verification.

Efforts are ongoing to comprehensively analyse the database, aiming to clarify the effects of the RDP on health outcomes, including weight loss, glycaemic control and retinal changes associated with hypertension and diabetes. With over 55 000 retinal images available, many recorded over time in individual patients, we have a unique opportunity to investigate the direct influence of the RDP on retinal features and potential correlations with overall health and survival. This invaluable resource promises to provide crucial insights into the multifaceted impact of intense dietary interventions on health outcomes and lifespan.

Strengths and limitation

The RDP was a clinical programme, and one of its limitations was the absence of an untreated control group. Another limitation is the lack of preserved biological specimens for verification of markers. In addition, the frequency of monitoring and measurement of markers was not systematic and uniform, varying among participants who voluntarily attended the programme for different durations and diverse health conditions. This, along with the fact that techniques for monitoring health status evolved significantly over the duration of the RDP, led to the unavailability of some desirable data. Nonetheless, there are several strengths of the RDP database. It features a large patient population, a long median programme stay (162; 60–724 days), and frequent use of 24-hour UCl concentration to document dietary adherence features that are difficult to replicate in experimental trials. The detailed and frequent measurements of many biological markers, including retinal images over an extended period, allow for investigation into the progression of various health conditions and markers over time.

CONCLUSION

The RDP database offers valuable insights into the effects of an extremely low sodium, protein, fat and cholesterol diet on various health indicators and survival outcomes. Our initial analysis suggests that the RDP effectively reduced BPs and increased life expectancy in patients with severe hypertension. We aim to make this database accessible to the broader scientific community. Currently, we are examining the RDP's effects on BPs, diabetes control and weight loss, as well as exploring the association of retinal features and BP changes using machine learning. This manuscript describes the baseline characteristics of the RDP participants and demonstrates the database's potential for more intricate future analyses.

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Contributors RS and PE contributed to the concept of the manuscript, drafted and analysed the data, DL and WM organised and provided data for analysis, JF, BB, SS, FN, AK, Y-JL, FCL, PK and CLorenz contributed to the design of the manuscript, provided critical input to analyses, interpretation of results, review and edits, SF, AG, EG, CLippert, MP and TR conducted the OCR analysis under CLippert supervision and provided review to the manuscript, AB assisted with data acquisition and specifically provided data on survival, P-HL oversaw the project, contributed to the concept and design and provided critical input to interpretation, review and edits. P-HL is the guarantor of the manuscript. ChatGPT was used for parts of the main text to make sure of proper grammar.

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Patient consent for publication Not applicable.

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