



# 库珀中心纵向研究:有氧运动的灵魂

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**摘要:** 目的:为肯尼斯·库珀(Kenneth H. Cooper)于 1970 年提出的库珀中心纵向研究(CCLS)提供详细历史。方法:对库珀中心纵向研究人群和库珀诊所所检查的重要参数,以及库珀诊所患者的各种疾病发病率和死亡率进行数据描述。并对近 50 年来已发表的库珀中心纵向研究的主要研究结果进行总结。结果:在库珀诊所检查期间,通过最大跑台运动测试客观地测量出的心肺功能(CRF)已成为各种疾病发病率和死亡率的强大且独立的风险因素。更具体地说,库珀中心纵向研究明确表明,中高水平的心肺功能与人体全因、心血管疾病和癌症死亡率有显著相关关系。此外,已经证明,中年人群的心肺水平是全因痴呆、Ⅱ型糖尿病、慢性肾病、癌症发病率和存活率以及一些其他慢性疾病的预测因子。因此,库珀中心纵向研究结果还表明,中年人群的心肺水平与老年时期的医疗保健成本呈显著相关。结论:除罕见情况以外,已经进行了近 50 年的库珀中心纵向研究的研究结果表明,相对于较低水平的心肺功能,中高水平的心肺功能可以有效预防许多疾病。

**关键词:** 心肺健康;发病率;死亡率

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## The Cooper Center Longitudinal Study: The Soul of Aerobics

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**Abstract:** Purpose: To provide a detailed history of the Cooper Center Longitudinal Study (CCLS), which was conceived of by Kenneth H. Cooper, MD, MPH in 1970. Methods: We describe the CCLS population, key components of the Cooper Clinic examination, and additional sources of morbidity and mortality data for Cooper Clinic patients. We also describe some of the major findings from the CCLS that have been published in peer-reviewed journals over the past half-century. Results: Cardiorespiratory fitness (CRF), which is measured objectively via a maximal treadmill exercise test during the Cooper Clinic exam, has emerged as a very powerful and independent risk factor for various morbidity and mortality outcomes. More specifically, CCLS has definitively shown that moderate to high levels of CRF provide a significant level of protection from all-cause, cardiovascular disease, and cancer mortality. Furthermore, we have shown that CRF at midlife is a very strong predictor of all-cause dementia, type 2 diabetes, chronic kidney disease, cancer incidence and survival, as well as several additional chronic health conditions. Accordingly, the CCLS has also shown that midlife CRF is significantly associated with health care costs later in life. Conclusion: With rare exception, regardless of the outcome being studied over the past half-century, the CCLS has shown that moderate to high levels of CRF provide substantial protection from many adverse health outcomes, relative to having a low level of CRF.

**Key Words:** cardiorespiratory fitness; morbidity; mortality

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## 0 前言

规律性的体力活动能够有效降低多种类型疾病发病率和死亡率。虽然,从目前来看,大家已经对这两者的关系达成了共识,但几十年前几乎没有任何证据支持这一观点。20 世纪 50 年代末到 60 年代肯尼斯·库珀(Kenneth H. Cooper)博士在美国空军任职期间,确信经常锻炼是预防疾病和保持身体健康的关键之一。他于 1970 年 12 月建立库珀研究所,因为他知道只有精心设计的研究才能证明他认定的事实。因此,当库珀诊所在此后不久刚刚开业时,库珀博士开始对客户进行细致记录,并有远见地意识到需要追踪这些客户的发病率和死亡率。于是,有氧运动中心纵向研究(Aerobics Center Longitudinal Study, ACLS)诞生了,ACLS 的主要目的是检查预防医学中心的心肺健康(Cardiorespiratory fitness, CRF)与健康结果之间的关系。值得注意的是,之前与运动相关的研究主要集中在身体活动的行为方面,而那时身体活动是通过问卷调查估算的。与身体活动不同,心肺健康可以通过最大跑台运动测试(Maximal Treadmill Exercise Testing)客观测量。在 ACLS 启动时,并没有关于心肺健康水平与重要健康结果之间关联的文献数据。因此,最大跑台运动测试很快成为 ACLS 的一个组成部分。

## 1 ACLS 与库珀中心纵向研究之间的差异

ACLS 是评估健康生活方式选择与各种结果(包括疾病、残疾和死亡率)之间关系的高效资源。库珀中心纵向研究(Cooper Center Longitudinal Study, CCLS)代表了 ACLS 的成熟和扩展版本,增加了变量、生物材料和更多的结果(截至 2014 年的新增的死亡率,医疗保险数据和德克萨斯癌症登记处数据)。CCLS 的整体样本量明显大于 ACLS,因此具有更多的发病率和死亡率数据。

两个研究的数据之间也存在其他重要差异。CCLS 数据集额外包含血液指标(包括维生素 D 水平、Omega-3 指数、肝炎筛查),老年人筛查[包括蒙特利尔认知评估(Montreal Cognitive Assessment, MoCA)和起立行走测试(Get Up and Go)评估],高敏感性心肌肌钙蛋白 T 水平,以及遗传物质。有关 CCLS 中新增内容的更多详细信息参见下文。

目前,有 112 789 名客户累计访问库珀诊所达 314 991 次,已经进行了近 250 000 次最大跑台运动测试;库珀诊所有着世界上最大的心肺健康数据库。CCLS 具有许多独特且非常宝贵的特性:客户通常是健康的、数据库相当大、进行长期随访。此外,仍需强调的是,最大跑台运动测试提供了 CRF 的客观

## 0 Background

Regular physical activity provides substantial protection against many types of morbidity and mortality. While this seems intuitive today, there was little evidence to support this opinion several decades ago. During his time in the U.S. Air Force in the late 1950's and 1960's, Dr. Kenneth Cooper became convinced that regular exercise was one of the keys to disease prevention and good health. He chartered The Cooper Institute in December, 1970 because he knew that only well-designed research studies would prove what he already believed to be true. Accordingly, when the Cooper Clinic first opened shortly thereafter, Dr. Cooper began to keep meticulous records of his patients and had the foresight to realize the need to track these patients for morbidity and mortality over time. Hence, the Aerobics Center Longitudinal Study (ACLS) was born. The major purpose of the ACLS was to examine the relationship between cardiorespiratory fitness and health outcomes in a preventive medicine center. It is important to note that previous exercise-related studies focused on physical activity, which is a behavior. At that time, physical activity was estimated by utilizing questionnaires. Unlike physical activity, cardiorespiratory fitness is a characteristic that can be objectively measured via maximal treadmill exercise testing. At the time the ACLS was launched, there was no data in the literature regarding the association of cardiorespiratory fitness level with important health outcomes. Thus, the maximal treadmill exercise test quickly became an integral portion of the ACLS.

## 1 Differences between the Aerobics Center Longitudinal Study and the Cooper Center Longitudinal Study

The Aerobics Center Longitudinal Study (ACLS) was a very productive resource in evaluating relationships between healthy lifestyle choices and a variety of outcomes including disease, disability, and mortality. The Cooper Center Longitudinal Study (CCLS) represents a matured and expanded version of the ACLS with added variables, biomaterials, and added outcomes (additional mortality through 2014, Medicare data, and Texas Cancer Registry). The overall sample size for



测量结果。正如顶尖的健康专家们经常说的那样：“你几乎可以到任何地方去研究病人，但 CCLS 是你唯一可以研究健康人的地方。”

## 2 CCLS 人群

库珀诊所的客户主要来源于自主入诊人群，尽管大约三分之一的客户是由其雇主推介而来。该诊所每年诊断客户 6 000~8 000 名，其中 75% 的客户是回访人群。临床访问者之间的问诊间隔各有不同。一般而言，老年客户往往比年轻客户更频繁地回访。超过 90% 的临床客户同意参加 CCLS。值得注意的是，库珀诊所的客户并不代表美国人口的随机样本。库珀诊所客户主要是非西班牙裔白人，受过高等教育，并且具有中上等级的社会经济地位。在 CCLS 数据库中，男性的数量多于女性，比例约为 3:1。因此，就整体美国人口的普适化而言，数据和研究结果存在一些局限性。然而，研究表明，CCLS 参与者的 CRF 水平与美国一般人群的 CRF 水平非常接近<sup>[1,2]</sup>。图 1 显示了 CCLS 男性和女性的最大 MET 值代表的 CRF，与选择参加国家健康和营养检验调查 (National Health and Nutrition Examination Survey, NHANES) 的男性和女性的随机样本相比较的结果。

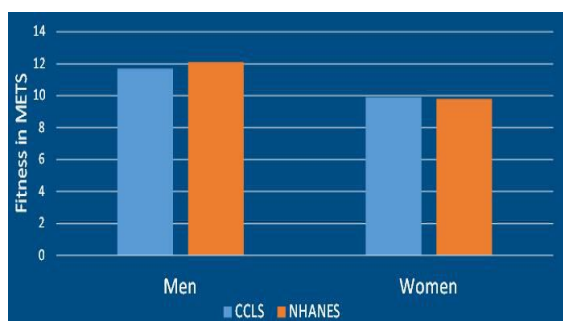


图 1 CCLS 男性和女性的最大 MET 值代表的 CRF 与选择参加国家健康和营养检验调查中男性和女性的随机样本比较

Figure 1 CRF Displayed as Maximal MET Values for CCLS Men and Women as Compared to A Random Sample of Men and Women Who Were Selected to Participate in NHANES

## 3 库珀诊所检查

库珀诊所检查的指标根据客户的年龄、性别和健康状况而有所不同。因为对每个客户都收集数千个变量，本文只提及一些最重要的变量。在完成知情同意后，有关年龄、性别、婚姻状况、种族、教育程度、当前和之前的吸烟状况、饮酒、就业状况、当前和之前的健康状况和症状、家族病史、饮食习惯、身体活动的信息（频率、强度、持续时间和类型）、访问次数、

CCLS is significantly larger than ACLS, and thus has a much greater amount of morbidity and mortality data.

Other important differences between the two data sets exist. The CCLS data set contains additional blood variables including vitamin D levels, the Omega-3 Index, hepatitis screens; geriatric screening including the Montreal Cognitive Assessment (MoCA) and Get Up and Go assessment; high sensitivity cardiac troponin T levels; and genetic material and. More detail regarding the additional information contained in the CCLS is provided below.

At the present time, there have been 314 991 Cooper Clinic visits by 112 789 patients. Nearly 250 000 maximal treadmill exercise tests have been administered; this represents the largest cardiorespiratory fitness database in the world. The CCLS has many unique and invaluable features. Patients are generally healthy, the data base is quite large, and there has been long-term follow-up. Additionally, it is important to reinforce that the maximal treadmill exercise test provides an objective measure of cardiorespiratory fitness (CRF). As is often stated by leading health experts, “You can go almost anywhere to study sick people; the CCLS is the only place you can go to study healthy people.”

## 2 The CCLS Population

Cooper Clinic patients are primarily self-referred, although approximately one-third are referred by their employer. The Clinic sees between 6 000 and 8 000 patients per year; 75% of whom are currently return patients. There are variable intervals between Clinic visits. Generally speaking, older patients tend to have their return visits more frequently than younger patients. Over 90% of Clinic patients consent to participate in the CCLS. We note that our patients do not represent a random sample of the United States population. Cooper Clinic patients are primarily non-Hispanic white, highly educated, and from middle to upper socioeconomic status. Within the CCLS database, men outnumber women by a margin of approximately 3 to 1. Thus, there are some limitations to our data and research findings in terms of generalization to the United States population as a whole. However, studies have shown that the CRF level among CCLS participants is very similar to that of the general United States population<sup>[1, 2]</sup>. The Figure be-



访问原因、安全习惯、心理状态和药物使用情况等信息均通过大范围的医疗问卷收集。虽然自 2008 年以来,药物使用情况已经常规地包含在数据库中,但数据库目前尚未提供诊所早期的药物使用情况。体重情况通过测量身体质量指数 (Body mass index, BMI) 和体脂百分比来确定。从历史上看,诊所也采用流体静力学评估体脂。血液检查包括但不限于总胆固醇, HDL 和 LDL 胆固醇, 甘油三酯, 葡萄糖, 肝脏、肾脏和甲状腺功能, 电解质, C 反应蛋白 (C-reactive protein, CRP), 同型半胱氨酸, 维生素 D 和 B12, 前列腺特异性抗原 (Prostate specific antigen, PSA), 总睾酮, 全血细胞计数 (Complete blood count, CBC), Omega-3 指数和血红蛋白 A1c。尿液分析用以测量 pH 值、比重和酮类变量, 以及确定样品中是否存在葡萄糖或蛋白质, 库珀诊所还会进行视力、听力和肺功能测试。

库珀诊在做最大跑台运动测试时所采用改良的 Balke 方案<sup>[3]</sup>, 其运动持续时间比更常用的 Bruce 方案更长。库珀博士更喜欢改良的 Balke 方案, 因为它可以非常缓慢地增加负荷、更安全, 并且比 Bruce 方案能提供更多的心电图 (Electrocardiograms, ECG) 和血压读数。由于改良的 Balke 方案比 Bruce 方案花费的时间更长, 因此可以更清晰地分析健康水平。改良的 Balke 跑台方案如下: 第 1 分钟速度为 88 m/min, 0% 坡度; 第 2 分钟速度为 88 m/min, 2% 坡度, 此后每分钟, 坡度增加 1%, 从第 25 min 开始坡度不变, 速度每分钟增加 5.4 m/min。在跑台运动测试期间收集的变量包括静息心率和血压, 以及静息心电图。在运动测试期间和之后, 收集关于心率、血压和 ECG 反应的数据。跑台的最终速度和等级用于计算最大 MET 值, 后者又反过来被用于确定基于年龄和性别的心肺健康类别。

客户也可以进行影像学检查, 把其作为临床检查的一部分。自 1997 年以来, 库珀诊所已对超过 40 000 名客户进行了超过 77 000 次计算机断层扫描。对这部分人群进行了广泛监测, 以确定其纵向心血管健康状况, 并结合 CCLS 中的其他成像研究 (包括 DEXA 扫描、超声心动图和颈动脉研究)。一个生物资料库 (Biobank) 从 2008 年 9 月开始运行, 以建立一个 DNA 和血液样本制品档案, 用以进行基于与健康生活选择相关的基因环境相互作用的研究。这项工作可以识别出与负责常见疾病有关的基因, 并了解常见疾病治疗和预防情况。目前, 库珀研究所存储的 DNA 和冷冻血浆中存有超过 13 000 件个人标本。

在库珀诊所获取的 CCLS 数据不是基于系统的

low shows CRF displayed as maximal MET values for CCLS men and women as compared to a random sample of men and women who were selected to participate in the National Health and Nutrition Examination Survey (NHANES)

### 3 The Cooper Clinic Exam

The parameters of the Cooper Clinic exam vary according to the patient's age, gender, and health status. Because there are thousands of variables collected for each patient, only some of the most important ones will be mentioned here. After completing an informed consent, information regarding age, gender, marital status, ethnicity, education level, current and prior smoking status, alcohol use, employment status, current and prior health status and symptoms, family history of disease, dietary habits, physical activity (frequency, intensity, duration, and type), visit number, reason for visit, safety habits, psychological status, and medication use are collected via an extensive medical questionnaire. While medication use has been routinely included in the database since 2008, medication use from the early years of the Clinic is not currently available in the database. Body mass index (BMI) and percent body fat are measured to determine body weight status. Historically, the Clinic also using hydrostatic assessment of body fat. Blood tests include, but are not limited to total cholesterol, HDL and LDL cholesterol, triglycerides, glucose, liver, kidney, and thyroid function, electrolytes, C-reactive protein (CRP), homocysteine, vitamins D and B-12, prostate specific antigen (PSA), total testosterone, complete blood count (CBC), Omega-3 Index, and hemoglobin A1c. Urinalysis is done to measure the variables of pH, specific gravity, and ketones, as well as to determine if glucose or protein is present in the sample. Tests of vision, hearing, and pulmonary function are also performed.

The Cooper Clinic uses the modified-Balke protocol<sup>[3]</sup>, which has a longer exercise duration than the more commonly used Bruce protocol. Dr. Cooper prefers the modified-Balke protocol because it increases workload very gradually, is safer, and allows time for a greater number of electrocardiograms (ECG) and blood pressure readings than the Bruce protocol. Because the modified-Balke test takes longer than the Bruce test, it



研究方案,而是基于前文提到的预防性健康评估和客户特定的临床建议,因此造成了随访问隔的可变性以及所有变量不同程度的可用性。正如前文所述,客户回访没有特定的时间间隔。此外还存在包括客户在访问时通常是健康的,但只有在他们生病时才重返诊所等挑战。CCLS 数据库由库珀研究所维护,该组织是一个非营利性的独立研究中心,其总体研究目标是评估生活方式行为和特征对健康的影响。库珀研究所执行严格的隐私保护措施。数据收集和知情同意过程每年均需要由库珀研究所的机构伦理审查委员会审查和批准。

## 4 死亡率监测

截至 2014 年 12 月 31 日,通过 NDIPlus(国家死亡指数)提供的信息,CCLS 涉及的人群中有 14 546 人死亡。与美国人口的整体情况相似,CCLS 中最常见的死亡原因是心血管疾病和癌症。

## 5 发病率监测

库珀中心除了使用回访期间收集的数据外,还使用回信调查进行发病率监测。中心在 1982 年、1986 年、1990 年、1995 年、1999 年、2001 年和 2004 年向所有研究涉及到的人群邮寄了大量问卷。并于 2011 年向接受电子束断层扫描检查的人群发送了一份调查问卷。多年来问卷的回收率为 50%~75%。受访者未完成调查的最常见原因是花费了太多时间、客户不感兴趣,或客户已搬家且没有更新地址。

### 5.1 医疗保险(Medicare)

1971—2009 年在库珀诊所接受检查的大约 29 000 名 CCLS 参与者获得了从 1999 年至 2009 年的医疗保险资格,并与医疗保险和医疗补助服务中心(Centers for Medicare and Medicaid Services, CMS)的数据库相匹配。该群组的可用数据包括医疗保险和医疗补助服务中心提供的经过算法验证的慢性病症库中的疾病诊断和最早病兆出现日期。还有个人国际疾病分类-9 信息(International Classification of Diseases-9)和住院及门诊索赔的编码及费用等其他可用信息。医疗保险数据为其他 CCLS 发病率监测提供了独特的补充,并有可能回答有关生活方式和预防对健康老龄化、生活质量和医疗系统资源利用模式的长期影响的问题。值得注意的是,医疗保险数据本质上是行政性的,并不代替临床诊断的结果或详细的医疗记录。例如,从医疗保险数据中提取的中风或高血压的诊断不能提供血压测量或诊断时的任何其他检查结果。此外,由于医疗保险数据仅在 1999—2009 年可用,因此通常难以获取 65 岁以上参与者

results in a clearer distribution of fitness levels. The modified-Balke treadmill protocol is as follows: minute 1: 88 meters/minute, 0% elevation, minute 2: 88 meters/minute, 2% elevation. Each minute thereafter, a 1% increase in elevation occurs. At 25 minutes, speed is increased by 5.4 meters/minute each minute. Variables collected during the treadmill exercise test include resting heart rate and blood pressure, as well as resting ECG. During and following the exercise test, data on heart rate, blood pressure, and ECG responses are collected. The final speed and grade of the treadmill are used to calculate maximal MET values, which in turn are used to determine cardiorespiratory fitness category based on age and gender.

Patients may also undergo imaging studies as part of their Clinic exam. Since 1997, the Cooper Clinic has conducted more than 77 000 computed tomography scans on over 40 000 patients. Extensive surveillance has been conducted on this sub-population to ascertain their longitudinal cardiovascular health status. Other imaging studies that are incorporated into the CCLS include DEXA scans, echocardiograms, and carotid artery studies. A biobank has been in operation since September, 2008 to establish an archive of DNA and blood product samples for research based on gene environment interaction related to healthy lifestyle choices. This effort can allow identification of genes responsible for common diseases and insights into their treatment and prevention. Currently, there are more than 13 000 individuals with specimens in the collection consisting of DNA and frozen plasma stored at The Cooper Institute.

Data acquired at the Cooper Clinic for the CCLS are not based on a systematic research protocol but rather on the previously mentioned preventive health evaluations and patient-specific clinical recommendations, resulting in variable follow-up intervals as well as different degrees of availability of all variables. As previously stated, there is no specific time interval between Cooper Clinic visits. Other challenges include the fact that patients are generally healthy at the time of their visit, and do not return to the Clinic only when they are ill. The CCLS database is maintained by The Cooper Institute, a nonprofit, independent research center with the overarching research goal of assessing the effect of



的完整医疗保险体验。

## 5.2 德克萨斯州癌症登记处

CCLS 获得了德克萨斯州癌症登记处的数据,其中包括 1995 年至 2007 年期间德克萨斯州居民的 CCLS 被研究者中发生癌症事件的信息,这些数据确定了约 6 100 例癌症。

## 6 心肺健康的健康益处

在过去 47 年中,CCLS 数据显示,具有中高水平的心肺功能与许多重要的健康益处相关,包括降低全因、心血管和癌症死亡率。从发病率的角度来看,保持健康与降低冠心病、中风、II 型糖尿病、代谢综合征、高血压、某些癌症、抑郁症和记忆丧失的风险有关。下文将对这些研究进行充分讨论。

## 7 心肺健康与冠状动脉危险因素

20 世纪 70 年代早期,有一些证据表明身体活动对冠心病具有保护作用,但其机制在很大程度上是未知的。库珀博士是研究平均年龄为 45 岁的 3 000 名男性(他们在 1970—1974 年间进行了检查<sup>[4]</sup>)客观测量的心肺功能(Cardiorespiratory fitness, CRF)与冠状动脉危险因素之间关联的第一人。根据年龄和最大跑台运动测试表现,将男性 CRF 按五分位数(Quintile)分为 5 类,在 CRF 五分位数人群上分组检查总胆固醇、甘油三酯、葡萄糖、血压、体脂百分比和静息心率。观察到 CRF 与所有这些变量之间呈负相关。即使将 CRF 的最低五分位数与下一个最高五分位数进行比较,也可以显示出这种关系。这是第一项报告客观测量的心肺功能与冠状动脉危险因素关联性的研究,也是 ACLS 的第一篇论文。

## 8 CRF 和全因死亡率

1989 年,库珀研究所和库珀诊所的研究人员发表了被认为具有里程碑意义的 CCLS 论文<sup>[5]</sup>。该论文发表在美国医学会杂志(JAMA)上,报告了 13 344 名平均年龄为 45 岁的男性和女性在基线综合预防性检查后接受了超过 8 年的随访。根据他们的最大跑台运动测试表现,以及年龄和性别,对每个客户的 CRF 按五分位数进行分类,Quintile1 代表低水平 CRF,Quintile2-3 和 Quintile4-5 分别代表中等水平 CRF 和高水平 CRF。在随访期间,有 283 名全因死亡。在随访期间发现基线 CRF 与死亡风险之间存在显著的负相关,换句话说,与基线时低 CRF 的男性和女性相比,在基线时中高水平 CRF 的男性和女性

lifestyle behaviors and characteristics on health outcomes. Privacy precautions are maintained through The Cooper Institute policies. The data collection and informed consent processes are reviewed and approved annually by the Institutional Review Board at The Cooper Institute.

## 4 Mortality Surveillance

Using the NDIPlus (National Death Index) service, 14 546 deaths were recorded in the CCLS population through December 31, 2014. Similar to the entire U.S. population, the most common causes of death in the CCLS are cardiovascular disease and cancer.

## 5 Morbidity Surveillance

In addition to using data collected during return visits, mail-back surveys are utilized for morbidity surveillance. Extensive questionnaires were mailed to the entire cohort in 1982, 1986, 1990, 1995, 1999, 2001, and 2004. In 2011, a questionnaire was sent to the Electron Beam Tomography cohort. The response rate was 50% ~75% throughout the years. The most common reasons given for not completing the survey were that it took too much time, the patient was not interested, or the patient moved and we did not have their new address.

### 5.1 Medicare

Approximately 29 000 CCLS participants examined at the Cooper Clinic between 1971-2009 who became eligible for Medicare between 1999 and 2009 were matched with the database at the Centers for Medicare and Medicaid Services (CMS). Data available for this subset of the cohort include disease diagnoses and earliest indication dates from the Chronic Condition Warehouse based on validated algorithms from the Centers for Medicare and Medicaid Services. Also available are individual International Classification of Diseases-9 and procedural codes for inpatient and outpatient claims as well as charges and other utilization information. Medicare data provides a unique complement to other CCLS morbidity surveillance and has the potential to answer questions regarding the long-term impact of lifestyle and prevention on patterns of healthy aging, quality of life, and healthcare

在随访期间死亡的可能性大大降低。当对 Quintile1 和 Quintile2 进行比较时, 显示出风险差异最大, 这是第一项明确证明 CRF 是男性和女性全因死亡率的重要且独立预测因子的研究。

## 9 CRF, 冠状动脉钙化和心血管事件

近年来, 冠状动脉钙化 (Coronary artery calcium, CAC) 评分一直是研究者预测未来心血管疾病发生风险的主要研究课题。虽然 CRF 和 CAC 分别对心血管疾病发生风险预测有很大贡献, 但令人惊讶的是, 人们对 CRF 如何影响不同类别 CAC 的心血管疾病风险仍知之甚少。考虑到这一点, 1998 年至 2007 年间检测的 8 425 名年龄在 30~80 岁之间的健康库珀诊所男性样本中检查这些关系<sup>[6]</sup>, 对他们的综合检测包括测量 CRF 的最大跑台运动测试、确定 CAC 评分的 CT 扫描, 以及传统心血管疾病危险因素的仔细测量。跟踪样本时间平均为 8.4 年, 在此期间发生了 383 个致命和非致命的心血管疾病发生案例。CAC 评分为 0 的男性心血管疾病发生风险发生率非常低 (1 000 人每年发生 1.3 次事件), 而 CAC 评分  $\geq 400$  的男性心血管疾病发生风险发生率则大大增高 (1 000 人每年发生 18.9 次事件)。根据以前的研究, 这一结果是预料之中的。一项包括 CRF 的新的研究结果如图 2 所示, 图 2 显示了基线检查后 15 年内 4 个 CAC 类别在不同 CRF 水平的心血管疾病发生风险, 最大年龄至 70 岁。在每个 CAC 类别中, 心血管疾病发生风险随着 CRF 水平的增加而降低。在 CAC 评分较高的男性中, CRF 风险降低更为明显。如图 2 所示, CAC 评分为 0 的非常健康的男性疾病发生风险最低, 而 CAC 评分  $\geq 400$  的非常不健康的男性疾病发生风险最高。需要强调的是, 较高水平的 CRF 可在所有 4 种 CAC 类别中对心血管疾病发生风险提供一定程度的保护。

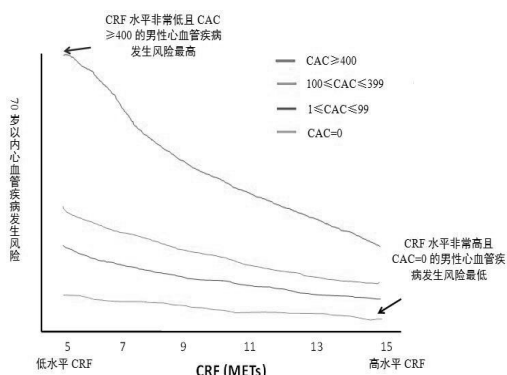


图 2 基线检查后 15 年内 4 个 CAC 类别在不同 CRF 水平的心血管疾病发生风险

Figure 2 Risk of CVD Events by Age 70 by CAC Score

system resource utilization. It is important to note that Medicare data is administrative in nature and does not represent a substitute for clinically adjudicated outcomes or detailed medical records. For example, a diagnosis of stroke or hypertension extracted from Medicare data cannot provide blood pressure measurement or any other exam results at the time of diagnosis. Also, since Medicare data is available only for an 11 year period beginning in 1999, the complete Medicare experience of a participant from age 65 is generally not captured.

## 5.2 Texas Cancer Registry

Data from the Texas Cancer Registry has been obtained with information on incident cancer cases among CCLS patients who were Texas residents between 1995 and 2007. With this data, we identified approximately 6 100 incident cancers.

## 6 Health Benefits of Cardiorespiratory Fitness

Over the past 47 years, CCLS data has shown that having a moderate to high level of measured cardiorespiratory fitness is associated with a number of significant health benefits. These include lower all-cause, cardiovascular, and cancer mortality. From a morbidity perspective, being fit is associated with a decreased risk of coronary heart disease, stroke, type 2 diabetes, metabolic syndrome, hypertension, certain cancers, depression, and memory loss. We will discuss many of these studies in the following text.

## 7 Cardiorespiratory Fitness and Coronary Risk Factors

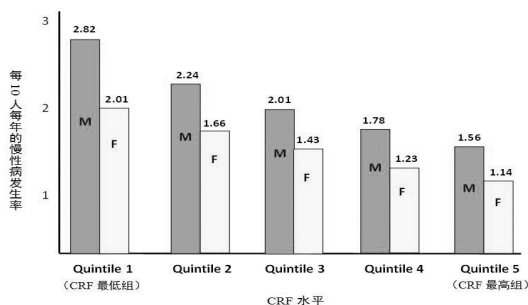
By the early 1970's there was some evidence that physical activity was protective against coronary heart disease, but the mechanisms were largely unknown. Dr. Kenneth Cooper was the first to examine the association between objectively measured cardiorespiratory fitness (CRF) and coronary risk factors in 3 000 men with a mean age 45 years who were examined between 1970 and 1974<sup>[4]</sup>. Men were divided into 5 categories (quintiles) of CRF based on their age and maximal treadmill exercise test performance. Total cholesterol, triglycerides, glucose, blood pressure, percent body fat, and resting heart rate were examined across CRF quintiles.





## 10 中年CRF与慢性病的发展

年龄的增长与心脏病和糖尿病等几种慢性疾病的发展密切相关。2012年,我们检查了中年CRF与老年非致命性慢性病发展之间的关系<sup>[7]</sup>。研究对象来自库珀诊所的18 670名看起来健康的男性和女性组成,平均年龄为49岁,他们接受了基线预防性检查,并确定可以在1999—2009年期间接受医疗保险,共研究了8种慢性病(Chronic conditions, CC):充血性心力衰竭、缺血性心脏病、中风、糖尿病、慢性阻塞性肺病、慢性肾病、阿尔茨海默病和结肠癌或肺癌。将受试者按CRF的五分位数分类,从基线检查开始的平均随访时间为26年。将最低CRF五分位数的男性与CRF最高五分位数的男性进行比较,未来CC的发生比率分别为每年每10人出现了2.82和每年每10人出现了1.56/10人。将最低CRF五分位数的女性与最高CRF五分位数的女性进行比较,未来CC的比率分别为每年2.01/10人和1.14/10人。因此,中年时较高水平的CRF与晚年患慢性病的风险降低显著相关,见图3。



注:柱状图顶端数字表示慢性病发生率,M为男性,F为女性。  
图3按CRF水平高低分为5组的18 670名健康中年男性和女性的慢性疾病发生率

Figure 3 Rate of Chronic Conditions by Midlife CRF Measurement in 18 670 Healthy Men and Women

## 11 中年CRF与全因痴呆症

随着美国人口平均年龄的持续增加,全因痴呆症已成为老年人的主要健康问题。因此,库珀诊所检查了中年CRF与全因痴呆未来发展风险之间的关联,这一点已经过医疗保险数据验证<sup>[8]</sup>。研究对象为包括19 458名健康男性和女性,平均年龄为49岁。将受试者按CRF的五分位数分类,在25年的随访期间,发生了1 659例全因痴呆病例。CRF最高分位数的受试者发生全因痴呆的可能性比最低五分位数的受试者低36%。重要的是,这是第一项显示中年CRF与未来全因痴呆风险之间显著相关的研究。

An inverse association between CRF and all of those variables was observed. This relationship was shown for most variables even when comparing the lowest quintile of CRF with the next highest quintile. This was the first study to report on these associations, and also represents the first ACLS paper.

## 8 CRF and all-cause Mortality

In 1989, Cooper Institute and Cooper Clinic researchers published what is considered the landmark CCLS paper<sup>[5]</sup>. Published in the Journal of the American Medical Association, this study reported on 13 344 men and women with an average age of 45 years who were followed for just over 8 years following their baseline comprehensive preventive exam. Based on their maximal treadmill exercise test performance, as well as age and sex, each patient was placed into quintiles of CRF. Quintile 1 represents low CRF, while quintiles 2-3 and 4-5 represent moderate and high CRF, respectively. There were 283 all-cause deaths during the follow-up period. A strong inverse relationship between baseline CRF and risk of death was found during follow-up. In other words, men and women who were moderately-to-highly fit at baseline were substantially less likely to die during the follow-up when compared to men and women who were low fit at baseline. The greatest reduction in risk was seen when comparing the lowest fit group (quintile 1) with the next lowest fit group (quintile 2). This was the first study to definitively prove that CRF is a significant and independent predictor of all-cause mortality in men and women.

## 9 CRF, Coronary Artery Calcium, and Cardiovascular Events

In recent years, coronary artery calcium (CAC) score has been a major topic of interest with regard to predicting future cardiovascular events. Although CRF and CAC each contribute strongly to prediction of these events, surprisingly little is known regarding how CRF impacts cardiovascular disease risk across different categories of CAC. With this in mind, we sought to examine these relationships in a sample of 8 425 generally healthy Cooper Clinic men between the ages of 30 and 80 who were examined between 1998 and 2007<sup>[6]</sup>.





## 12 中年健身和慢性肾病

慢性肾病(Chronic kidney disease, CKD)在老年人群和糖尿病客户中很常见。使用 CCLS 和医疗保险数据,我们检查了中年 CRF 与 CKD 发生风险的关系<sup>[9]</sup>。研究对象包括 17 979 名健康男性和女性,平均年龄为 50 岁,在 1971 年至 2009 年期间接受检查,并在 1999—2009 年接受医疗保险。在每年 116 973 人的医疗保险追踪中共发生 2 022 例 CKD,与较低健康水平者相比,中等水平和高水平 CRF 研究对象发生 CKD 的可能性分别低 24% 和 34%,即使在随访期间患上糖尿病的客户中,CRF 每增加 1 MET,CKD 的风险也会降低 6%。

## 13 中年CRF 与中风风险

在美国,中风是造成长期残疾的主要原因,也是导致死亡的主要原因之一。尽管低水平的 CRF 已成为中风的一个强大且独立的危险因素<sup>[10]</sup>,但尚不清楚这种相关性在何种程度上可通过糖尿病、高血压和心房颤动等中风危险因素的发展来解释。库珀诊所检查了中年 CRF 与 65 岁以后中风风险之间的关系,并排除上述风险因素的影响<sup>[11]</sup>,共有 19 815 名在基线时平均年龄为 50 岁的库珀诊所客户参与了该研究。所有人看起来都很健康,且在检验时中风风险相对较低。基于他们的跑台运动测试表现,将每个个体划分为低、中或高 CRF 类别。共有每年 129 436 人的医疗保险随访数据,在此期间发生了 808 例中风住院治疗案例。重要的是,在分析中还仔细考虑了在临床检查时可能未检测的中风时的高血压、糖尿病或心房颤动的数据。使用低 CRF 组作为对照组,在医疗保险随访期间,中年时期中等水平 CRF 和高水平 CRF 研究对象因中风住院治疗的可能性分别为 24% 和 37%。重要的是,这些数字是在考虑了基线时出现的中风危险因素以及中风诊断时出现的中风危险因素后确定的。因此,无论在研究期间的任何时间是否存在高血压、糖尿病或心房颤动,CRF 仍然是中风住院风险的很有效的预测因子。

## 14 中年CRF 与癌症发病率和癌症存活率

癌症是美国第二大死亡原因。CRF 与癌症以及癌症诊断后的存活率在很大程度上是未知的。库珀诊所试图通过利用 CCLS 和医疗保险数据来检查中年 CRF 与肺癌、前列腺癌和结直肠癌之间的关系,以及中年 CRF 与癌症诊断后存活率的关系<sup>[12]</sup>。1971—2009 年期间,库珀诊所共检查了 13 949 名男性,平均年龄为 49 岁。男性按 CRF 水平分为低、

Their comprehensive exam included a maximal treadmill exercise test to measure CRF, a CT scan to determine CAC score, as well as careful measurement of traditional cardiovascular disease risk factors. The sample was followed for an average of 8.4 years, during which time 383 fatal and non-fatal cardiovascular events occurred. While men with CAC scores of 0 had a very low rate of cardiovascular events (1.3 events per 1 000 person-years), men with CAC scores of >400 had a much higher rate (18.9 events per 1 000 person-years). Based on previous studies, this finding was expected. A more novel finding is shown in the Figure below. The Figure shows the risk of cardiovascular events up to the age of 70 across CRF level in the 4 CAC categories over a 15 year period following the baseline exam. Within each CAC category, the risk of cardiovascular events decreased across increasing levels of CRF. The decrease in risk across CRF was more pronounced among men with higher CAC scores. As the Figure shows, the lowest risk was seen in very highly fit men with CAC scores of 0, while the highest risk was seen in very low fit men with CAC scores >400. What is important to reinforce is that higher levels of CRF provide some degree of protection against cardiovascular events in all 4 CAC categories.

## 10 Midlife CRF and Development of Chronic Conditions

Older age is strongly associated with development of several chronic conditions such as heart disease and diabetes. In 2012, we examined the association of midlife CRF and the development of non-fatal chronic conditions in older age<sup>[7]</sup>. The sample consisted of 18 670 apparently healthy Cooper Clinic men and women with an average age of 49 years, who received a baseline preventive exam and survived long enough to receive Medicare coverage from 1999-2009. Eight chronic conditions (CCs) were studied: congestive heart failure, ischemic heart disease, stroke, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, Alzheimer's disease, and colon or lung cancer. Subjects were placed into quintiles of CRF as previously described. The average length of follow-up from the time of the baseline exam was 26 years. When comparing men in the lowest CRF quintile to men in the high-



中、高组。与低水平 CRF 的男性相比,高水平 CRF 的男性罹患肺癌和结直肠癌的可能性分别低 55% 和 44%。然而,CRF 较高的男性患前列腺癌的可能性比较低健康程度男性高 22%。CRF 每增加 1 MET,肺癌和结直肠癌发病风险分别降低 17% 和 9%。我们推测,较高健康程度男性的前列腺癌发病率较高的原因可能是由于与较低健康程度男性相比,该组中有着更频繁的医疗保健筛查。在医疗保险年龄范围内被诊断患有癌症的男性中,观察到与较低健康程度男性相比,较高健康程度的男性癌症死亡率降低了 32%,而且心血管疾病死亡率降低了 68%。

## 15 中年 CRF 与心力衰竭住院治疗

心力衰竭(Heart failure, HF)是美国 65 岁及以上人群住院治疗的最常见原因之一。通过结合 CCLS 数据与医疗保险数据,库珀诊所在 19 485 名男性和女性中检查了中年 CRF 与因 HF 住院产生的 CRF 变化之间的关系<sup>[13]</sup>。在对基线检查的传统 HF 风险因素进行调整后,较高水平 CRF 与 HF 住院风险的降低有关,每增加 1 MET 的跑台运动测试成绩, HF 住院风险降低 18%。一部分客户(n=8 683)接受了第二次检查,距基线检查的平均时间为 4.2 年。在基线检查时健康(Quintile2-5)且持续保持健康的个体后续 HF 住院的风险最低。相反,在基线检查时不健康(Quintile1)且仍持续不健康的个体 HF 住院的风险最高。基线时不健康但进行随访检查时恢复健康的个体有中等程度的 HF 住院治疗风险。

## 16 CRF 与肥胖和心力衰竭死亡率

虽然已有文献报道了身体活动与心力衰竭之间的关联,但迄今为止没有研究检查过客观测量的 CRF 与心力衰竭死亡率之间的关系。库珀诊所追踪了 44 674 名库珀诊所男性,平均年龄为 19.8 岁<sup>[14]</sup>。在基线检查时,所有男性看起来都很健康,按 CRF 水平分为低、中、高组,且基于标准 BMI 类别被分类为正常体重、超重或肥胖。在随访期间,有 153 名男子死于 HF,与高 CRF 男性相比,中等和低 CRF 男性因 HF 死亡的可能性分别高 1.63 倍和 3.97 倍。与正常体重男性相比,超重和肥胖男性因 HF 死亡的可能性分别高 1.56 和 3.71 倍。在正常体重和超重类别中,中高 CRF 男性死于 HF 的可能性大大低于低 CRF 男性。此外,在具有相同数量 HF 风险因素的男性中,中高 CRF 男性死于 HF 的可能性大大低于低 CRF 男性。例如,对于有 1 个 HF 危险因素的男性来说,低 CRF 男性死于 HF 的可能性是中高 CRF 男性的 4 倍。

est CRF quintile, the rate of future CC's was 2.82 versus 1.56 per 10 person-years, respectively. When comparing women in the lowest CRF quintile to women in the highest CRF quintile, the rate of future CC's was 2.01 versus 1.14 per 10 person-years, respectively. Thus, higher levels of CRF at midlife were significantly associated with a reduced risk of developing chronic conditions later in life. See Figure below.

## 11 Midlife CRF and all-cause Dementia

As the average age of the U.S. population continues to increase, all-cause dementia has become a major health issue among older adults. Accordingly, we examined the association between midlife CRF and the future risk of developing of all-cause dementia as verified by Medicare data<sup>[18]</sup>. The sample included 19 458 healthy Cooper Clinic men and women with a mean age of 49 years. Subjects were placed into quintiles of CRF as described previously. During a 25 year follow-up period, 1 659 cases of all-cause dementia occurred. There was a decreased risk of dementia across quintiles of CRF, with subjects in the highest CRF quintile 36% less likely to develop all-cause dementia than subjects in the lowest quintile. Importantly, this was the first study to show a significant association between midlife CRF and the future risk of all-cause dementia.

## 12 Midlife Fitness and Chronic Kidney Disease

Chronic kidney disease (CKD) is common among the older population as well as those with diabetes mellitus. Using CCLS as well as Medicare data, we examined the association of midlife CRF and subsequent risk of CKD<sup>[19]</sup>. The sample consisted of 17 979 apparently healthy men and women with a mean age of 50 years, who were examined between 1971 and 2009, who also received Medicare coverage from 1999 to 2009. A total of 2022 cases of incident CKD occurred during 116 973 person-years of Medicare follow-up. Individuals with moderate and high CRF were 24% and 34% less likely, respectively, to develop CKD when compared to those who were low fit. Even among those who developed diabetes mellitus during follow-up, the risk of CKD was reduced by 6% per 1-MET increment in CRF.



## 17 健康行为和长期医疗保健费用

### 17.1 老年CRF与医疗保健费用

虽然普遍认为中年心血管危险因素与以后的医疗保健成本相关,但与这些风险因素无关的 CRF 对医疗保健成本影响的数据仍旧匮乏。研究了 19 571 名健康男性和女性,平均年龄为 49 岁,他们在库珀诊所接受检查,随后在 1999—2009 年期间接受了医疗保险<sup>[15]</sup>,按 CRF 水平分为低、中、高组。医疗保险的平均随访时间为 6.5 年,共计每年 126 388 人的数据。当比较中年高水平 CRF 和低水平 CRF 的参与者时,男性(分别为 7 569 美元、12 811 美元)和女性(分别为 6 065 美元、10 019 美元)的平均年度医疗保健费用显著降低。根据心血管危险因素进行调整后,CRF 每增加 1 MET,男性和女性的平均年度医疗保健费用分别降低 6.8% 和 6.7%。

### 17.2 简单生活 7 要素(Life's Simple 7)与长期医疗保健费用

美国心脏协会开发了“Life's Simple 7”,囊括了与心血管健康密切相关的行为和因素<sup>[16]</sup>。包括饮食、身体活动、吸烟、体重指数、血液胆固醇、血糖和静息血压。每个要素分为较差、中等或理想 3 个水平。把 7 要素达到理想水平的状态定义为理想的心血管健康。为了评估这 7 个要素的经济影响,对 1999—2009 年期间入选医疗保险的 4 906 名库珀诊所平均年龄为 56 的中年男性和女性样本进行了评估<sup>[17]</sup>。根据他们的基线检查结果,将他们分为 3 个等级:(1)不利,具有 0~2 项理想心血管健康特征;(2)中等,具有 3~4 项理想心血管健康特征;(3)有利,具有 5~7 项理想心血管健康特征。不到 1% 的参与者具有所有 7 个理想特征,而 14.8% 的男性和 30.1% 的女性被划分为有利组。不利组的年均非心血管疾病医疗保险费用为 5 058 美元,而有利组为 3 883 美元。年均心血管疾病费用中也有相同趋势(不利组和有利组分别为 1 344 美元及 778 美元)。因此,在中年期间具有更多数量的理想心血管健康特征与晚年的医疗保健成本成显著负相关。

## 18 CRF 与代谢综合征的发生率

代谢综合征(Metabolic syndrome, MetSyn)是一种常见病症,具有以下至少 3 项表现:高腰围、低 HDL 胆固醇、血液甘油三酯水平升高、血糖水平升高和静息血压升高。患有 MetSyn 的个体全因和心血管死亡的风险增加。CCLS 以前的研究表明,中高 CRF

## 13 Midlife CRF and Risk of Stroke

Stroke is the leading cause of long-term disability in the U.S., and is also among the leading causes of death. Although low levels of CRF have emerged as a strong and independent risk factor for stroke<sup>[10]</sup>, it is not known to what extent this association is explained by development of stroke risk factors such as diabetes, hypertension, and atrial fibrillation. We examined the association of midlife CRF and risk of stroke after the age of 65 years, independent of these risk factors<sup>[11]</sup>. A total of 19 815 Cooper Clinic patients with an average age of 50 years at baseline participated in the study. All were apparently healthy, with a relatively low risk of stroke at the time of their exam. Based on their treadmill test performance, each individual was placed into low, moderate, or high CRF categories as previously described. There were a total of 129 436 person-years of Medicare follow-up data, during which time 808 stroke hospitalizations occurred. Importantly, data regarding the presence of hypertension, diabetes, or atrial fibrillation at the time of the stroke that may not have been present at the time of the Clinic exam was also carefully considered in the analyses. Using the low CRF group as the referent, patients with moderate and high CRF at midlife were 24% and 37% less likely to be hospitalized for stroke, respectively, during the period of Medicare follow-up. Importantly, these numbers were determined after taking baseline stroke risk factors into account, as well as stroke risk factors that were present at the time the stroke was diagnosed. Thus, independently of whether or not hypertension, diabetes, or atrial fibrillation was present at any time during the study, CRF remained a strong predictor of stroke hospitalization risk.

## 14 Midlife CRF, Cancer Incidence, and Cancer Survival

Cancer is the second leading cause of death in the U.S. The association between CRF and incident cancer, as well as survival following a diagnosis of cancer is largely unknown. We sought to examine the association of midlife CRF and incident lung, prostate, and colorectal cancer, as well as the association of midlife CRF with survival following a cancer diagnosis by utilizing



女性与低 CRF 女性 MetSyn 的发生率更低<sup>[18]</sup>。该研究的目的是确定健康人的基线 CRF 是否是 MetSyn 的预测因子。1979—2003 年期间,共有 9 007 名男性和 1 491 名女性在基线检查时没有 MetSyn; 他们的平均年龄是 44 岁,按 CRF 水平划分为低、中和高 3 组。在平均 5.7 年的随访期间,1 346 名男性和 56 名女性患上了 MetSyn。与低 CRF 男性相比,中高 CRF 水平男性罹患 MetSyn 的可能性分别为 26% 和 53%。与低 CRF 女性相比,中高 CRF 水平女性发展 MetSyn 的可能性分别为 20% 和 63%<sup>[19]</sup>。这项研究首次表明,低水平 CRF 是男性和女性 MetSyn 的有效因子,因此,在许多情况下,可以通过简单地实现中等至高水平的 CRF 来预防 MetSyn。

## 19 CRF, 肥胖与死亡率

虽然体重状态和 CRF 都是重要的健康指标,但这是第一项旨在比较 CRF 与体重状态在死亡风险方面重要性的 CCLS 研究<sup>[20]</sup>。将 25 389 名库珀诊所男性样本分为低、中、高 3 种 CRF 类别,同时还被分为正常体重、超重和肥胖的 BMI 类别,以研究上述两因素与死亡风险之间的关系。在平均 8.5 年的随访期间共有 673 人死亡。在每个 BMI 类别中,在 CRF 水平较高的情况下,全因死亡率的风险显著降低。因此,即使在超重和肥胖男性中,较高水平的 CRF 也可以降低死亡率。这是第一项显示 CRF 与死亡率相关性高于 BMI 的研究。因此,在所有 BMI 类别中都可以看到具有中高水平 CRF 的益处。这项重要的研究为许多未来探讨“健康与肥胖”问题的 CCLS 研究奠定了基础。

## 20 CRF 与心血管风险分类

心血管疾病 (Cardiovascular disease, CVD) 是导致居住在生活水平较高的国家的成年人死亡的主要原因之一。CVD 的传统影响因素包括血胆固醇水平升高、高血压、吸烟、糖尿病、年龄、家族史、不活动和肥胖。在过去的 30 年中,低水平的 CRF 已经成为一个非常强大和独立的 CVD 风险因素。尽管已经开发出许多预测未来心血管疾病风险的公式,但这些公式都没有把 CRF 水平包括在共识的风险因素中。事实上,CRF 通常是在体检期间非常规测量的唯一主要风险因素。本研究的目的是确定当加入传统危险因素时,CRF 在多大程度上能降低 CVD 的风险<sup>[21]</sup>。研究共有 66 371 名库珀诊所男性和女性接受了全面的基线检查,按 CRF 水平进行分类。样本平均跟踪时间为 16 年,在此期间 CVD 导致 1 621 例死亡。

CCLS and Medicare data<sup>[12]</sup>。A total of 13 949 men with a mean age of 49 years were examined at the Cooper Clinic between 1971 and 2009. Men were placed into low, moderate, and high CRF categories as previously described. When compared to men with low CRF, men with high CRF were 55% and 44% less likely to develop lung and colorectal cancer, respectively. However, men with high CRF were 22% more likely to develop prostate cancer than low fit men. Each 1-MET increase in CRF was associated with a 17% and 9% reduction in risk of incident lung and colorectal cancer, respectively. We speculate that the reason for the higher incidence of prostate cancer in high fit men may be due to more frequent health care screening among this group as compared to low fit men. Among men diagnosed with cancer at Medicare age, we observed a 32% reduction in cancer mortality, and a 68% reduction on cardiovascular disease mortality in high fit men as compared to low fit men.

## 15 Midlife CRF and Heart Failure Hospitalization

Heart failure (HF) is the most common reason for hospitalization in the U.S. among individuals ages 65 and older. By linking CCLS data with Medicare data, we examined the associations of midlife CRF and change in midlife CRF with HF hospitalizations in a group of 19 485 men and women<sup>[13]</sup>. Following adjustment for traditional HF risk factors at the baseline examination, higher CRF was associated with an 18% lower risk for HF hospitalization per 1-MET increment in treadmill test performance. A subset of patients (n=8, 683) underwent a second exam, with a mean period of 4.2 years after the baseline exam. Individuals who were fit as baseline (Quintiles 2-5) and remained fit had the lowest risk for subsequent HF hospitalization. Conversely, individuals who were unfit at baseline (Quintile 1) and remained unfit had the highest risk for HF hospitalization. Individuals who were unfit as baseline, but fit at the follow-up exam had an intermediate risk for HF hospitalization.

## 16 CRF, Adiposity, and Heart Failure Mortality

While associations between physical activity and



正如预期的那样,男性和女性的 CRF 水平与 CVD 死亡风险降低有关。接下来,使用传统的风险因素,如年龄、静息血压、血胆固醇水平、糖尿病和吸烟,来预测样本中 CVD 死亡的风险。当 CRF 被添加到预测公式中时,方程的准确性得到显著改善。换句话说,了解客户的 CRF 水平可以让医生更好地评价他们的 CVD 发生风险。该研究与许多其他 CCLS 论文一起,有助于建议美国心脏协会将心肺健康测量作为一个评价 CVD 发生风险的重要标志<sup>[21]</sup>。

## 21 CRF与Ⅱ型糖尿病的发病率

目前美国成年人中肥胖和Ⅱ型糖尿病的流行程度处于历史最高水平。肥胖和缺乏身体活动是Ⅱ型糖尿病的两个主要原因。因为 CRF 的客观测量比自我报告的身体活动更能预测健康水平<sup>[22]</sup>,试图确定 CRF 和 BMI 在库珀诊所女性中Ⅱ型糖尿病发病率的独立和联合相关性<sup>[23]</sup>。该样本由 6 249 名看起来健康的女性组成,平均年龄为 44 岁,样本分为低、中、高 3 种 CRF 类别,同时还被分为正常体重、超重和肥胖的 BMI 类别。在 17 年的随访期间,共发生了 143 例Ⅱ型糖尿病病例。与低 CRF 女性相比,那些中高 CRF 女性患Ⅱ型糖尿病的风险分别降低了 14% 和 39%。超重或肥胖的人患有糖尿病的风险分别为正常体重的个体的 2.6 倍和 4.6 倍。在正常体重的女性中,低水平 CRF 与Ⅱ型糖尿病发病风险增加无显著相关。然而,在超重和肥胖女性中,低水平 CRF 的Ⅱ型糖尿病风险增加 3.6 倍。最后,在超重和肥胖组中,与超重和肥胖但 CRF 属于中高水平的女性相比,低 CRF 的女性患Ⅱ型糖尿病的风险显著增加。这些结果强调了定期进行体育锻炼和维持正常体重在预防Ⅱ型糖尿病方面的重要性。

## 22 结语

库珀研究所和库珀诊所已经成立了 50 周年,在此期间收集的大量信息意义非凡。由于库珀博士在库珀研究所和库珀诊所成立时的远见卓识,CCLS 数据库目前收集了大约 113 000 名客户的详细健康信息,这些客户经历了近 250 000 次最大跑台运动测试。由于跑台测试为 CRF 提供了的客观测量,已经能够检查 CRF 与各种发病率和死亡率结果的相关性。除极少数案例外,无论研究何种健康结果,都证明了相对于低水平 CRF,具有中高水平的 CRF 可实质性预防多种疾病。正如库珀博士常说的那样:“如果定期运动的益处可以做成药丸,它将是自有史以来被最广泛使用和最有用的药方。”

heart failure have been reported in the literature, no study to date had examined the association of objectively measured CRF and heart failure mortality. We followed 44 674 Cooper Clinic men over an average period of 19.8 years<sup>[14]</sup>. At baseline, all of the men were apparently healthy. Participants were assigned to low, moderate, and high CRF categories as described previously, and were classified as normal weight, overweight, or obese based on standard body mass index (BMI) categories. During the follow-up period, 153 men died from HF. Compared with high fit men, moderate and low fit men were 1.63 and 3.97 times more likely to die from HF, respectively. Compared to normal weight men, overweight and obese men were 1.56 and 3.71 times more likely to die from HF, respectively. Within the normal weight and overweight categories, fit men were substantially less likely to die from HF than unfit men. Additionally, among men with the same number of risk factors for HF, fit men were substantially less likely to die from HF than unfit men. For example, among men who had 1 risk factor for HF, unfit men were about 4 times more likely to die from HF than fit men.

## 17 Healthy Behaviors and Long-Term Health Care Costs

### 17.1 CRF and Health Care Costs in Later Life

While it is accepted that cardiovascular risk factor burden in middle age is associated with health care costs later in life, data regarding the effect of CRF on health care costs independent of these risk factors is lacking. We studied 19 571 apparently healthy men and women with an average age of 49 years who were examined at Cooper Clinic and subsequently received Medicare coverage from 1999 to 2009<sup>[15]</sup>. CRF was categorized as low, moderate, and high as previously described. There was a mean Medicare follow-up of 6.5 years, resulting in 126 388 person-years of data. When comparing participants with high CRF at midlife to those with low CRF, average annual health care costs were significantly lower in men (\$7 569 vs. \$12 811) and women (\$6 065 vs. \$10 019). When adjusted for cardiovascular risk factors, average annual health care costs were 6.8% and 6.7% lower



in men and women, respectively, per 1-MET increment in CRF.

## 17.2 Life's Simple 7 and Long-Term Health Care Costs

The American Heart Association developed "Life's Simple 7" which includes behaviors and factors that strongly relate to cardiovascular health<sup>[16]</sup>. These include healthy diet, physical activity, smoking, body mass index, blood cholesterol, blood glucose, and resting blood pressure. Each component is categorized as either poor, intermediate, or ideal. Ideal cardiovascular health is defined by having ideal levels of each of the 7 components. In order to evaluate the economic impact of these 7 factors, a sample of 4 906 Cooper Clinic middle-aged men and women with a mean baseline age of 56 who were enrolled in Medicare between 1999 and 2009 were evaluated<sup>[17]</sup>. Subjects were categorized into one of three cardiovascular health profile groups according to their baseline exam: 1) Unfavorable (0-2 ideal cardiovascular health characteristics) 2) Intermediate (3-4 ideal cardiovascular health characteristics) 3) Favorable (5-7 ideal cardiovascular health characteristics). Less than 1% of participants had all 7 ideal characteristics, while 14.8% of men and 30.1% of women scored in the Favorable group. The mean annual non-cardiovascular disease Medicare costs in the Unfavorable group was \$5 058 versus \$3 883 in the Favorable group. A similar trend was seen for mean annual cardiovascular disease costs (\$1 344 versus \$778 in Unfavorable vs. Favorable groups, respectively). Thus, having a greater number of ideal cardiovascular health components in middle-age is associated with significantly lower Medicare costs in later life.

## 18 CRF and Incidence of Metabolic Syndrome

Metabolic syndrome (MetSyn) is a common condition characterized by any three or more of the following: high waist circumference, low HDL cholesterol, elevated blood triglyceride level, elevated blood glucose level, and elevated resting blood pressure. Individuals with MetSyn are at increased risk for all-cause and cardiovascular mortality. Previous work in the CCLS

had shown that MetSyn was much less common among fit women than unfit women<sup>[18]</sup>. The purpose of this study was to determine whether baseline CRF in healthy persons was a predictor of incident MetSyn. A total of 9 007 men and 1 491 women who did not have MetSyn at baseline were evaluated between 1979 and 2003; their average age was 44 years. Patients were placed into categories of low, moderate, and high CRF as previously described. During an average follow-up period of 5.7 years, 1346 men and 56 women developed MetSyn. When compared to low fit men, moderate and high fit men were 26% and 53% less likely to develop MetSyn, respectively. When compared to low fit women, moderate and high fit women were 20% and 63% less likely to develop MetSyn, respectively<sup>[19]</sup>. This study was the first to show that a low baseline level of CRF is a strong predictor of incident MetSyn in both men and women. Thus, in many cases MetSyn might be prevented by simply achieving a moderate to high level of CRF.

## 19 Fitness, Fatness, and Mortality

While body weight status and CRF are each important health markers, this was the first CCLS study to examine the relative importance of CRF versus body weight status with regard to mortality risk<sup>[20]</sup>. A sample of 25 389 Cooper Clinic men was divided into CRF categories of low, moderate, and high based as previously described. They were also divided into body mass index (BMI) categories of normal weight, overweight, and obese based on criteria at that time. All possible combinations of CRF and BMI were made in order to examine their relative contribution to mortality risk. A total of 673 deaths occurred during an average 8.5 year follow-up period. Within each category of BMI, there was a significantly lower risk of all-cause mortality across increasing levels of CRF. Thus, even in overweight and obese men, higher levels of CRF were protective against mortality. This was the first study to show that CRF is more strongly associated with mortality than BMI. Thus, the benefits of having a moderate to high level of CRF are seen across all BMI categories. This important study helped set the stage for many future CCLS studies examining the 'fitness versus fatness' issue.



## 20 Cardiovascular Risk Classification and CRF

Cardiovascular disease (CVD) is the leading cause of death among adults residing in countries with a relatively high standard of living. Traditional risk factors for CVD include elevated blood cholesterol level, hypertension, smoking, diabetes, age, family history, inactivity, and obesity. Over the past three decades, a low level of CRF has emerged as a very powerful and independent risk factor as well. Although equations for predicting risk of future cardiovascular disease have been developed, these equations have historically excluded CRF level as a risk factor. In fact, CRF is often the only major risk factor that is not routinely measured during physical examinations. The purpose of this study was to determine to what extent CRF improves cardiovascular disease (CVD) risk classification when added to traditional risk factors<sup>[21]</sup>. A total of 66 371 Cooper Clinic men and women underwent a comprehensive baseline examination and were placed into categories of CRF as described previously. The sample was followed for an average of 16 years, during which time 1 621 deaths occurred as a result of CVD. As expected, there was a decreased risk of CVD mortality across higher CRF categories in both men and women. Next, traditional risk factors such as age, resting blood pressure, blood cholesterol level, diabetes, and smoking were used to predict the risk of CVD mortality in the sample. When CRF was added to the prediction equation, the accuracy of the equation was significantly improved. In other words, knowing a patient's level of CRF gives the physician a better measure of their cardiovascular risk status than including only the previously mentioned traditional risk factors. This paper, along with many other CCLS papers, was instrumental in convincing the American Heart Association to recommend including measurement of cardiorespiratory fitness as a vital sign<sup>[22]</sup>.

## 21 CRF and Incidence of Type 2 Diabetes

The current prevalence of obesity and type 2 diabetes among U.S. adults is at an all-time high. Both obesity and physical inactivity are two major contributors to type 2 diabetes. Because an objective measurement of CRF is a stronger predictor of health outcomes than self-reported physical activity<sup>[22]</sup>, we sought to de-

termine the independent and joint associations of CRF and BMI on the incidence of type 2 diabetes in Cooper Clinic women<sup>[23]</sup>. The sample consisted of 6 249 apparently healthy women with a mean age of 44 years. Participants were grouped by CRF category as previously described, and were also grouped by BMI using standard cut points. During 17 years of follow-up, there were 143 incident cases of type 2 diabetes. When compared to low fit women, those who were moderately or highly fit had a 14% and 39% decreased risk of incident type 2 diabetes, respectively. When compared with normal weight individuals, those who were overweight or obese had 2.6 and 4.6 times the risk of incident diabetes, respectively. Among normal weight women, low CRF was not associated with an increased risk of incident type 2 diabetes. However, in overweight and obese women, low CRF was associated with a 3.6-fold increase in risk of type 2 diabetes. Finally, within the overweight and obese groups, unfit women had a significantly increased risk of type 2 diabetes when compared to overweight and obese fit women. These results underscore the importance of regular physical activity and maintaining a normal body weight for prevention of type 2 diabetes.

## 22 Summary

As we approach the 50th anniversary of The Cooper Institute and Cooper Clinic, the sheer volume of information that has been collected over that time is quite extraordinary. Because of Dr. Cooper's foresight at the time that The Cooper Institute and Cooper Clinic were founded, the CCLS database currently houses detailed health information on approximately 113 000 patients who have undergone nearly 250 000 maximal treadmill exercise tests. Because the treadmill test provides an objective measure of CRF, we have been able to examine the association of CRF with a wide variety of morbidity and mortality outcomes. With rare exception, regardless of the outcome being studied, we have shown that having a moderate to high level of CRF provides substantial protection from many adverse health outcomes, relative to having a low level of CRF. As Dr. Cooper is fond of saying "If the benefits of regular exercise could be put into a pill, it would be the most widely used and most beneficial medication ever developed."





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